1: J Immunol Methods. 1995 Jan 27;178(2):173-81. Related Articles, Links

Entrez PubMed
PubMed Services
Related Resources

Characterization of the apoptotic effects of human tumor necrosis factor: development of highly rapid and specific bioassay for human tumor necrosis factor and lymphotoxin using human target cells.

Higuchi M, Singh S, Aggarwal BB.

Department of Clinical Immunology and Biological Therapy, University of Texas M. D. Anderson Cancer Center, Houston 77030.

Currently available bioassays for most cytokines require several days and therefore must be performed under sterile conditions. In this report we describe a bioassay for tumor necrosis factor (TNF) and lymphotoxin (LT) that is extremely rapid and specific and does not require sterile conditions. Using tritiated thymidine release, we could conveniently monitor degradation of DNA into small fragments following the incubation of human myelogenous leukemia ML-1a cells with TNF. The assay showed that TNF-dependent DNA fragmentation was potentiated by cycloheximide and occurred within 90 min. Treatment of cells to TNF lead to apoptosis as indicated by thymidine release, DNA laddering on agarose gels and morphological alterations. Under these conditions, plasma membrane were not damaged as indicated by lack of chromium release. This effect was linear with TNF concentration. This assay had high throughput, did not require sterile conditions, could be carried out in the absence of serum, and was sensitive only to TNF and LT and not to interferon (IFN)-alpha, IFN-beta, IFN-gamma, transforming growth factor beta, interleukin-4, leukemia inhibitory factor and granulocyte-monocyte colony stimulating factor; all cytokines known to inhibit different cell types. Besides detection of TNF in biological fluids, this assay may prove useful for the identification of novel inhibitors of TNF action.

PMID: 7836779 [PubMed - indexed for MEDLINE]

1: FASEB J. 1996 Feb;10(2):325-32. Related Articles, Links

Entrez PubMed

Tumor cell resistance to apoptosis due to a defect in the activation of sphingomyelinase and the 24 kDa apoptotic protease (AP24).

Wright SC, Zheng H, Zhong J.

Palo Alto Institute of Molecular Medicine, Mountain View, California 94043, USA.

PubMed Services

Signal transduction pathways involved in apoptotic cell death are poorly understood, although recent studies have implicated sphingomyelin hydrolysis and generation of the second messenger, ceramide. Previous work in this laboratory demonstrated that a serine protease termed AP24 was activated by TNF or UV light and induced DNA fragmentation in isolated nuclei. This study extended these findings to examine the role of these enzymes in apoptosis of the U937 cell line and the mechanism of resistance of its variant, U9-TR. Although this subclone was selected by growth in TNF, it was unexpectedly found to resist apoptosis induced by UV light, but was still sensitive to anti-Fas-induced DNA fragmentation. Here we show that in contrast to normal U937 cells, UV light and TNF both failed to activate neutral or acidic sphingomyelinase or AP24 in the U9-TR variant. However, anti-Fas activated both neutral and acidic sphingomyelinase in the variant comparable to that seen in parental U937. The U9-TR variant could be sensitized to TNF or UV light activation of both sphingomyelinase and DNA fragmentation by the protein phosphatase inhibitors okadaic acid and calyculin A. Furthermore, exogenous bacterial-derived sphingomyelinase caused U9-TR activation of AP24 and DNA fragmentation comparable to that in the parental U937. Exposure of permeabilized U937 cells to ceramide caused internucleosomal DNA cleavage that was blocked by an inhibitor of AP24. Taken altogether, these findings demonstrate that TNF or UV light activate sphingomyelinase that leads to the generation of ceramide resulting in activation of AP24 and DNA fragmentation in sensitive cells. A selective defect in signals leading to sphingomyelinase activation can confer resistance to apoptosis even though the variant is still sensitive to downstream apoptotic signals such as nuclear DNA fragmentation by activated exogenous AP24.

Related Resources

PMID: 8641566 [PubMed - indexed for MEDLINE]

1: J Exp Med. 1994 Aug 1;180(2):525-35. Related Articles, Links

Entrez PubMed
PubMed Services
Related Resources

Ionizing radiation acts on cellular membranes to generate ceramide and initiate apoptosis.

Haimovitz-Friedman A, Kan CC, Ehleiter D, Persaud RS, McLoughlin M, Fuks Z, Kolesnick RN.

Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York 10021.

Recent investigations provided evidence that the sphingomyelin signal transduction pathway mediates apoptosis for tumor necrosis factor alpha (TNF-alpha) in several hematopoietic and nonhematopoietic cells. In this pathway, TNF-receptor interaction initiates sphingomyelin hydrolysis to ceramide by a sphingomyelinase. Ceramide acts as a second messenger stimulating a ceramide-activated serine/threonine protein kinase. The present studies show that ionizing radiation, like TNF, induces rapid sphingomyelin hydrolysis to ceramide and apoptosis in bovine aortic endothelial cells. Elevation of ceramide with exogenous ceramide analogues was sufficient for induction of apoptosis. Protein kinase C activation blocked both radiation-induced sphingomyelin hydrolysis and apoptosis, and apoptosis was restored by ceramide analogues added exogenously. Ionizing radiation acted directly on membrane preparations devoid of nuclei, stimulating sphingomyelin hydrolysis enzymatically through a neutral sphingomyelinase. These studies provide the first conclusive evidence that apoptotic signaling can be generated by interaction of ionizing radiation with cellular membranes and suggest an alternative to the hypothesis that direct DNA damage mediates radiation-induced cell kill.

PMID: 8046331 [PubMed - indexed for MEDLINE]

1: Biochim Biophys Acta. 1995 Apr 6;1266(1):1-8. Related Articles, Links

Entrez PubMed
PubMed Services
Related Resources

Inhibition of lysosomal acid sphingomyelinase by agents which reverse multidrug resistance.

Jaffrezou JP, Chen G, Duran GE, Muller C, Bordier C, Laurent G, Sikic BI, Levade T.

Department of Medicine, Stanford University Medical Center, CA 94305, USA.

An increasing body of evidence appears to implicate the lipid bilayer of multidrug resistant (MDR) cells with P-glycoprotein activity. Several cationic amphiphilic drugs (CADs) have been extensively described as modulators of MDR. These same agents are also known to (1) inhibit lysosomal acid sphingomyelinase (ASmase), a phospholipid degrading enzyme, and/or (2) induce phospholipidosis in animal tissues or cultured cell lines. In this report, we randomly selected 17 CADs and evaluated their potency in modulating MDR in the murine MDR P388/ADR leukemia cell line. We compared these results with their ability to inhibit ASmase and observed a significant dose-dependent linear relationship (95% central confidence interval), between ASmase inhibition and MDR reversal. This approach permitted us to identify three new modestly potent chemosensitizers: trimipramine, desipramine, and mianserine. Modulation of MDR was not cell line specific, since CADs at 10 microM increased doxorubicin (DOX) and vinblastine (VBL) (but not methotrexate, MTX) cytotoxicity in both P388/ADR and the human MDR cell lines MES-SA/Dx5 and K562/R7, but not in the parental drug-sensitive cells. Although all chemosensitizing CADs at 10 microM significantly increased Rhodamine-123 (Rho-123) accumulation in the human leukemia MDR cell line K562/R7 and most presented significant displacement of the photoaffinity labelling probe iodoarylazidoprazosin, no correlation between these observations and the ability of CADs to sensitize MDR cells to DOX and VBL was found. In conclusion, our study strongly suggests that the chemosensitizing potency of agents such as CADs may be due to a dual mechanism of action: direct antagonism of P-gp activity and indirect modulation of P-gp activity through the disruption of cellular lipid metabolism.

PMID: 7718613 [PubMed - indexed for MEDLINE]

Display Abstract Show: 20 Sort Send to Text

1: Int J Cancer 1999 May 17;81(4):620-8 Related Articles, Books, LinkOut

Distinct p53-independent apoptotic cell death signalling pathways in testicular germ cell tumour cell lines.

Burger H, Nooter K, Boersma AW, van Wingerden KE, Looijenga LH, Jochemsen AG, Stoter G.

Department of Medical Oncology, University Hospital Rotterdam, Josephine Nefkens Institute, The Netherlands.

The induction of apoptosis by diverse apoptotic stimuli was studied in a panel of 6 testicular germ cell tumour (TGCT) cell lines with defined p53 status. Although the sensitivity to a particular stimulus varied considerably among the TGCT cell lines, the differences in response were not associated with the presence of functional p53. Mutant (mt) p53-expressing NCCIT and S2 (no p53 protein) were both readily triggered into apoptosis by cisplatin and doxorubicin, while wild-type(wt)-p53-transactivation-competent 2102 EP cells failed to undergo drug-induced apoptosis. Moreover, transactivation-deficient NCCIT cells and wtp53-expressing NT2 cells were equally sensitive to cisplatin, doxorubicin, gamma radiation, and cell-permeable C2-ceramide. Our p53 data suggest that, at least in this panel of non-isogeneic TGCT cell lines, hypersensitivity to therapeutic agents is not associated with p53 status. Next, we examined the impact of p53 inactivation on apoptosis induction in isogeneic NT2 sublines expressing human papillomavirus E6 protein. Evidently, abrogation of p53 function did not affect the hypersensitivity to apoptotic stimuli. We noted that drug-sensitive S2 cells were highly resistant to radiation-induced apoptosis, indicating distinct signalling pathways for chemotherapy and irradiation. The impaired radiation-induced apoptotic pathway in S2 and 2102 EP could not be restored by addition of cell-permeable C2-ceramide, suggesting that the blockade is downstream of ceramide generation. Ligation of Fas/APO-1/CD95 by anti-Fas effectively induced apoptosis in Fas-antigen expressing S2, 2102 EP and 833 KE. The efficient Fas-mediated activation of apoptosis in drug-, radiation-, and ceramide-resistant 2102 EP cells further suggests that diverse apoptosis-inducing factors may use distinct signalling pathways. In summary, we demonstrated the presence of distinct p53-independent apoptotic pathways in TGCT cells.

PMID: 10225454 [PubMed - indexed for MEDLINE]

1: Cancer Res 1994 Mar 15;54(6):1596-603

Differential sensitivity to the induction of apoptosis by cisplatin in proliferating and quiescent immature rat thymocytes is independent of the levels of drug accumulation and DNA adduct formation.

Evans DL, Tilby M, Dive C.

Cancer Research Campaign Cellular and Molecular Pharmacology Group, School of Biological Sciences, Manchester University, United Kingdom.

Immature rat thymocytes readily undergo apoptosis following exposure to many different stimuli, including agents which cause DNA damage, such as the topoisomerase II inhibitor etoposide and irradiation. We have shown previously that cells isolated from the immature rat thymus are resistant to the induction of apoptosis by the DNA-damaging agent cis-diamminedichloroplatinum(II) (cisplatin) (D. L. Evans and C. Dive, Cancer Res., 53:2133-2139, 1993). More than 85% of these thymocytes are quiescent. Here, we demonstrate that following purification of the minority subpopulation of thymocytes that are proliferating, a 2-h exposure to 50 microM cisplatin resulted in rapid apoptosis with 66% apoptotic cells by 12 h. In contrast, purified, nonproliferating thymocytes treated with cisplatin exhibited control levels of apoptosis at 12 h. Both proliferating and nonproliferating thymocytes rapidly underwent apoptosis following continuous exposure to methylprednisolone (10 microM) and etoposide (10 microM). The discrepancy in the levels of apoptosis seen in proliferating and quiescent thymocytes in response to cisplatin could not be attributed to changes in total cellular levels of cisplatin or to the number of DNA-platinum adducts which were determined, respectively, by atomic absorption spectrometry and competitive enzyme-linked immunoadsorbent assay. These results imply that in contrast to engagement of thymocyte apoptosis by methylprednisolone and etoposide, where apoptosis was proliferation independent, cisplatin-induced apoptosis depends on the presence of cells in S and G2-M phases of the cell cycle. Moreover, comparison of etoposide and cisplatin responses in thymocytes suggests that DNA damage per se may not be sufficient to induce apoptosis and that the type of DNA damage is important in this regard.

PMID: 8137265 [PubMed - indexed for MEDLINE]

1: FASEB J 1996 Aug;10(10):1147-58 Related Articles, Books, LinkOut

Lipid mediator networks in cell signaling: update and impact of cytokines.

Serhan CN, Haeggstrom JZ, Leslie CC.

Department of Anesthesia, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.

Biomembranes serve barrier functions and serve as a store for precursors of rapidly generated, structurally diverse intracellular and extracellular lipid-derived mediators (LM). Cell activation is accompanied by remodeling of membrane components that appear to be essential in signal transduction. Phospholipases (PLA2, PLC, PLD, sphingomyelinase) are pivotal in the generation of these LM including eicosanoids, platelet activating factor (PAF), diacylglycerides, ceramide, and other newly discovered bioactive autacoids. Cytokines exert a dramatic multilevel impact both in regulating enzymes in individual LM pathways and in generating LM central to their action. Here, we provide an overview and update of recent progress in this area with emphasis on the effect of cytokines on LM networks. The generation of eicosanoids (prostaglandins, leukotrienes, and lipoxins), oxygenated lipids, and PAF remain the focus of rational drug design targets given their established roles in cell-cell communication and as mediators in inflammation and pathophysiologic events. Key enzymes in these pathways are cloned, sequenced, and their subcellular organization is investigated with surprising findings implicating involvement of the nuclear membrane at the functional level. Several LM receptors are identified and cloned, and results from transgenic animals have emerged for several key enzymes. Novel bioactive eicosanoids were discovered, including 15-epi-lipoxins, isoprostanes, and isoleukotrienes, that offered new concepts to consider in formation of LM and the actions of nonsteroidal anti-inflammatory drugs. Together, these findings indicate that LM play critical and essential roles in both signal transduction and cell-cell communication and will continue to be important pathways to be considered in novel therapeutic approaches.-Serhan, C. N., Haeggstrom, J. Z., Leslie, C. C. Lipid mediator networks in cell signaling: update and impact of cytokines.

Publication Types:
- Review
- Review, Tutorial

1: Curr Opin Oncol 1998 Nov;10(6):552-9

The role of ceramide in the cellular response to cytotoxic agents.

Jarvis WD, Grant S.

Department of Medicine, Medical College of Virginia, Richmond 23298-0230, USA.

The sphingolipid messenger ceramide has been implicated in the initiation of apoptotic cell death in a variety of physiologic settings. Recent investigation has shown that ceramide-dependent stress signaling is associated with chemotherapy-related apoptosis. It is not entirely clear, however, whether drug-mediated generation of ceramide is essential for execution of the cell death program, or simply represents a component of the genotoxic stress response. For example, there is evidence that ceramide subserves an important role in certain stresses (e.g., ionizing radiation, daunorubicin) but represents a secondary process in others (e.g., cytarabine). The review presents evidence for and against a cytotoxic effector function for ceramide in the lethal actions of conventional antineoplastic agents.

Publication Types:
- Review
- Review, Tutorial

PMID: 9818235 [PubMed - indexed for MEDLINE]

1: Nat Genet. 1995 Jul;10(3):288-93. Related Articles, Links

Entrez PubMed
PubMed Services
Related Resources

Acid sphingomyelinase deficient mice: a model of types A and B Niemann-Pick disease.

Horinouchi K, Erlich S, Perl DP, Ferlinz K, Bisgaier CL, Sandhoff K, Desnick RJ, Stewart CL, Schuchman EH.

Department of Human Genetics, Mount Sinai School of Medicine, New York, New York 10029, USA.

Types A and B Niemann-Pick disease (NPD) result from the deficient activity of acid sphingomyelinase (ASM). An animal model of NPD has been created by gene targeting. In affected animals, the disease followed a severe, neurodegenerative course and death occurred by eight months of age. Analysis of these animals showed their tissues had no detectable ASM activity, the blood cholesterol levels and sphingomyelin in the liver and brain were elevated, and atrophy of the cerebellum and marked deficiency of Purkinje cells was evident. Microscopic analysis revealed 'NPD cells' in reticuloendothelial organs and characteristic NPD lesions in the brain. Thus, the ASM deficient mice should be of great value for studying the pathogenesis and treatment of NPD, and for investigations into the role of ASM in signal transduction and apoptosis.

PMID: 7670466 [PubMed - indexed for MEDLINE]

1: Cell. 1996 Jul 26;86(2):189-99.

Acid sphingomyelinase-deficient human lymphoblasts and mice are defective in radiation-induced apoptosis.

Santana P, Pena LA, Haimovitz-Friedman A, Martin S, Green D, McLoughlin M, Cordon-Cardo C, Schuchman EH, Fuks Z, Kolesnick R.

Laboratory of Signal Transduction, Memorial Sloan-Kettering Cancer Center New York, New York 10021, USA.

Stress is believed to activate sphingomyelinase to generate ceramide, which serves as a second messenger in initiating the apoptotic response. Conclusive evidence for this paradigm, however, is lacking. In the present study, we used a genetic approach to address this issue directly. We show that lymphoblasts from Niemann-Pick patients, which have an inherited deficiency of acid sphingomyelinase activity, fail to respond to ionizing radiation with ceramide generation and apoptosis. These abnormalities are reversible up on restoration of acid sphingomyelinase activity by retroviral transfer of human acid sphingomyelinase cDNA. Acid sphingomyelinase knockout mice also expressed defects in radiation-induced ceramide generation and apoptosis in vivo. Comparison with p53 knockout mice revealed that acid sphingomyelinase-mediated apoptosis and p53-mediated apoptosis are likely distinct and independent. These genetic models provide definitive evidence for the involvement of acid sphingomyelinase in one form of stress-induced apoptosis.

PMID: 8706124 [PubMed - indexed for MEDLINE]

Functions of Ceramide in Coordinating Cellular Responses to Stress

Yusuf A. Hannun

Sphingolipid metabolites participate in key events of signal transduction and cell regulation. In the sphingomyelin cycle, a number of extracellular agents and insults (such as tumor necrosis factor, Fas ligands, and chemotherapeutic agents) cause the activation of sphingomyelinases, which act on membrane sphingomyelin and release ceramide. Multiple experimental approaches suggest an important role for ceramide in regulating such diverse responses as cell cycle arrest, apoptosis, and cell senescence. In vitro, ceramide activates a serine-threonine protein phosphatase, and in cells it regulates protein phosphorylation as well as multiple downstream targets [such as interleukin converting enzyme (ICE)-like proteases, stress-activated protein kinases, and the retinoblastoma gene product] that mediate its distinct cellular effects. This spectrum of inducers of ceramide accumulation and the nature of ceramide-mediated responses suggest that ceramide is a key component of intracellular stress response pathways.

The author is in the Department of Medicine, Duke University Medical Center, Durham, NC 27710, USA.

The paradigm of signaling through the glycerophospholipids (1) has taught us a critical lesson in lipid-mediated signal transduction and cell regulation: The structural complexity of membrane glycerophospholipids belies the role they subserve in signal transduction. Second messengers derived from precursor glycerophospholipids include diacylglycerol (DAG), inositol trisphosphate (IP_3), arachidonate, the eicosanoids, and platelet activating factor. Individual glycerophospholipids can be viewed as stores of potential information released in response to cellular stimuli through the activation of specific enzymes. Messages are then carried by the released lipid-derived products in the form of specific interactions of these products with their targets [such as protein kinase C (PKC) or the IP_3 receptor].

Sphingolipids, which are structurally even more complex than the glycerophospholipids, also participate in signal transduction. Sphingolipids have roles in the response to cell contact, as receptor components, as anchors for proteins, and as markers of tumor progression and cell differentiation (2). Defects in several sphingolipid hydrolases result in the various forms of inherited sphingolipidoses (3). Sphingolipids also have an essential role in cell viability. In both *Saccharomyces cerevisiae* and

mammalian cells, mutations in the first enzyme of de novo sphingolipid biosynthesis (serine-palmitoyl transferase) result in abolition of sphingolipid formation and loss of viability that is reconstituted by replacement with sphingolipids (4). Several bacterial hemolysins and cytotoxins have been identified as sphingomyelinases, and toxic fungal metabolites (such as the fumonisins, the sphingofungins, and the australifungins) specifically target enzymes of sphingolipid metabolism (5); these findings further underscore the importance of sphingolipids in cell regulation.

Sphingosine, sphingosine-1-phosphate, and possibly other lysosphingolipids have potential roles in signal transduction (2, 6). This role has been best defined, however, for sphingomyelin and ceramide. The following review focuses on recent developments in ceramide metabolism and physiology and their implications for aspects of cell biology such as apoptosis, growth suppression, and the stress response.

Generation, Kinetics, and Magnitude of the Ceramide Signal

A number of extracellular inducers of sphingomyelin hydrolysis, ceramide accumulation, or both have been identified. Among these inducers are 1,25-dihydroxyvitamin D_3, tumor necrosis factor-α (TNF-α), endotoxin, interferon-γ, interleukin-1 (IL-1), Fas ligands, CD28, dexamethasone, retinoic acid, progesterone, ionizing irradiation, chemotherapeutic agents, heat, and nerve growth factor (NGF) (7). Ceramide concentrations are also elevated in cells infected with human immunodeficiency virus (8) and in senescent fibroblasts (9).

The kinetics of ceramide formation in response to these inducers are complex and variable; reported responses range from seconds to hours, and the same inducer has generated very different ceramide responses in different studies. This range of findings has become a major source of confusion as to the possible relevant roles of ceramide in signal transduction and cell regulation. Figure 1 is an idealized conglomeration of the results of studies of ceramide accumulation in response to various agonists. From this scheme, at least three different categories of ceramide responses can be discerned.

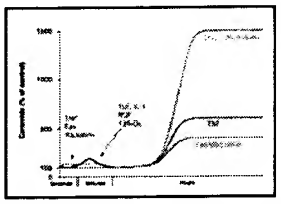

Fig. 1. Kinetics of ceramide formation. This is a composite scheme that illustrates three phases of ceramide formation (see text).
[View Larger Version of this Image (12K GIF file)]

Acute changes in ceramide concentration within seconds or within 1 to 2 min have been described primarily with TNF-α, ionizing radiation, and engagement of the Fas receptor (10). These changes may be indicative of a role for ceramide in mediating some of the very early responses to TNF-α, such as activation of nuclear factor κB (NF-κB). Such acute kinetics of ceramide are problematic for several reasons. First, the magnitude of the response has usually been modest, with increases on the order of 20 to 50% (Fig. 1). Second, these acute changes have not been detected in multiple other studies examining responses to TNF-α and Fas (11). Third, acute changes in ceramide (on the order of 50 to 100%) have been described that are caused by changes in culture conditions and exchange of media (12). Finally, the specificity of the ceramide effects implicated with these kinetics (for example,

activation of NF-κB and Raf-1) has not been examined, which raises the distinct possibility that ceramide per se may not be the relevant lipid mediator in these responses.

Intermediate and reversible kinetics of ceramide accumulation have been best documented with IL-1, TNF-α, 1,25-dihydroxyvitamin D_3, NGF, and several neurotrophins (13) that cause accumulation of ceramide over 5 to 120 min in a reversible manner. The relevance of these responses--in which ceramide concentrations may double--is not readily apparent because they occur after the earliest responses to IL-1 and TNF-α, such as activation of NF-κB.

Several extracellular stimuli and agents induce prolonged and persistent accumulation of ceramide that occurs over a period of several hours (Fig. 1). Serum withdrawal in leukemia cells results in a 15-fold accumulation of ceramide over 24 to 48 hours, and TNF-α and Fas activation also induce a three- to eightfold increase in intracellular concentrations of ceramide over 12 to 24 hours (11, 14). The magnitude of this response is more commensurate with cellular amounts of ceramides achieved when cells are exposed to exogenous short chain ceramides. This persistence of accumulation of ceramide raises the possibility of a reprogramming of cell function through a ceramide-activated pathway. Such a mechanism may be relevant to proposed roles for ceramide in growth suppression.

The sites of ceramide formation and the possible compartmentalization of signaling pools of sphingomyelin remain poorly understood. Sphingomyelin hydrolyzed in response to 1,25-dihydroxyvitamin D_3, NGF, or TNF-α is located in the plasma membrane (15), with several observations indicating localization on the inner leaflet. On the other hand, IL-1-induced sphingomyelin hydrolysis and ceramide formation colocalize with a caveolin-rich fraction. This pool of sphingomyelin resides on the outer leaflet of the plasma membrane (16). These studies underscore the possibility that distinct pools of sphingomyelin and ceramide exist and could participate in distinct pathways of cell regulation. No studies have examined the site of formation of the long and persistent phase of ceramide accumulation (Fig. 1).

Roles of Ceramide in Distinct Pathways of Cell Regulation

Recent discoveries have lent support to the principle that cells have intrinsic biochemical and molecular machinery that functions primarily to sense various forms of injury and insult and to execute appropriate programs of response. Mammalian cells respond to such stimuli primarily by undergoing cell cycle arrest to allow adequate time for repair of damage or by undergoing apoptosis (programmed cell death) if the damage is too severe and irreparable. It is also possible that other outcomes, such as terminal cell differentiation and senescence, represent a form of stress response.

Several lines of evidence suggest a role for ceramide in various forms of growth suppression and cell death. First, the spectrum of inducers of ceramide accumulation includes, and is perhaps limited to, most of the major inducers of apoptosis, terminal differentiation, or growth suppression. Growth factors do not appear to produce a similar response. Second, the changes in intracellular concentrations of ceramide in response to these extracellular agents precede the cellular effects of these agents on growth suppression. Third, treatment of cells with cell-permeable analogs of ceramide such as C2- and C6-ceramide has been shown to induce apoptosis, cell senescence, terminal differentiation, or cell cycle

arrest in several cell types (9, 14, 17). These effects of exogenous ceramides are specific to D-*erythro*-ceramide; D-*erythro*-dihydroceramide lacks any such activity. Dihydroceramide is a naturally occurring ceramide that lacks the 4-5 trans double bond but retains the stereochemical configuration of D-*erythro*-ceramide, and its uptake and metabolism are very similar to those of D-*erythro*-ceramide (18). Fourth, the cellular concentrations of C2- and C6-ceramide in cells exposed to 1 to 10 μM C2- or C6-ceramide is approximately 10 to 100 pmol per nanomole of phospholipid, which is comparable to the concentrations of ceramide achieved after prolonged response to TNF-α or serum deprivation (Fig. 1). Finally, indirect manipulation of endogenous amounts of ceramide also supports a role for ceramide in mediating apoptosis and growth arrest. For example, the addition of precursor gangliosides, precursor sphingosine, bacterial sphingomyelinase (which generates ceramide at the plasma membrane), D-*threo*-1-phenyl-2-decanoylamino-3-morpholino- 1-propanol (PDMP) (which inhibits further incorporation of ceramide into glycolipids), or D-*erythro*-2-(*N*-myristoylamino)-1-phenyl-1-propanol (D-MAPP) (which inhibits ceramide metabolism through ceramidase) results in accumulation of ceramide ranging from three to eight times the concentrations in unstimulated cells (19). These increased concentrations are similar to those observed in cells treated with TNF, Fas, or dexamethasone, or in cells deprived of serum. In all these cases, the addition of these agents is accompanied by apoptosis, cell cycle arrest, or both.

Ceramide, growth suppression, and cell cycle arrest. In several cell lines, ceramides and inducers of ceramide formation cause inhibition of thymidine uptake and induce a G_0/G_1 cell cycle arrest that is accompanied by early dephosphorylation of the retinoblastoma gene product (Rb) (14, 19, 20) (Fig. 2). Several lines of evidence suggest a necessary role for Rb in mediating cell cycle arrest in response to ceramide. Cells deficient in Rb (such as cell lines derived from retinoblastoma tissues) do not manifest cell cycle arrest in response to ceramide. Cells that do respond to ceramide become unresponsive when Rb is inactivated or sequestered by any of several Rb-binding proteins such as adenoviral E1a and large T of SV40. On the other hand, the absence of Rb does not appear to diminish the responsiveness of cells to the apoptotic effects of ceramide. Ceramide-independent pathways for the regulation of Rb also exist. For example, as fibroblasts or MCF-7 breast cancer cells enter quiescence, Rb becomes dephosphorylated without concomitant changes in ceramide (Fig. 2). Thus, ceramide may be involved preferentially in stress-induced dephosphorylation of Rb.

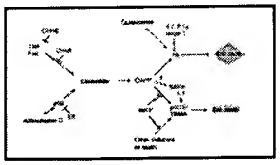

Fig. 2. Regulation of cell cycle arrest and apoptosis by ceramide. Various cytokines and extracellular agents (such as TNF and Fas) activate sphingomyelinases in a CrmA-inhibitable pathway. Other agents such as actinomycin D cause elevation of ceramide in a p53-dependent mechanism (55). The accumulated ceramide activates CAPP, which then can result in activation of Rb, which in turn mediates the effects of ceramide on cell cycle arrest. Alternatively, ceramide can activate proteases of the prICE/YAMA family, resulting in apoptosis. Various viral proteins (indicated in red) appear to target several key components of this pathway. [View Larger Version of this Image (10K GIF file)]

In addition, ceramide suppresses the expression of the c-*myc* protooncogene by interfering with transcription elongation (21). Ceramide also inhibits the cellular activation of phospholipase D (22).

Because phospholipase D and its immediate and sequential products (phosphatidic acid and DAG, respectively) are implicated as either mitogenic or viability factors, these results indicate that ceramide not only activates growth suppressor programs but may also interfere with proliferative signaling pathways.

Ceramide, proteases, Bcl-2, and the apoptotic response. In several malignant and nonmalignant cell lines, ceramide rapidly and specifically induces apoptosis while closely related lipids remain inactive (17, 23). Ceramide activates proteases (24) of the interleukin converting enzyme (ICE) family, especially prICE/YAMA/CPP32, the protease responsible for cleavage of poly- (adenosine diphosphate-ribose) polymerase (PARP). Activation of prICE by ceramide and induction of apoptosis are inhibited by overexpression of Bcl-2 (25, 26), which suggests that Bcl-2 functions downstream of ceramide. On the other hand, overexpression of Bcl-2 does not reduce the amounts of ceramide produced in response to extracellular agents (25) (Fig. 2). The effects of ceramide on prICE can be dissociated from activation of Rb, and vice versa (25); similarly, activation of PKC antagonizes the effects of ceramide on apoptosis but not on cell cycle arrest. Therefore, ceramide may relay a stress signal, whereby the specific cellular outcome (apoptosis or cell cycle arrest) appears to be determined by additional downstream modulators (such as Rb, Bcl-2, proteases, and PKC). Indeed, in some cell lines, ceramide may actually protect from apoptosis (27), possibly by preferentially steering cells into cell cycle arrest.

Other effects of ceramide. Although ceramide has been reported to activate the ERK1 and ERK2 members of the mitogen-activated protein (MAP) kinase family (28), the balance of current evidence suggests that ceramide may be more specifically coupled to stress-activated protein kinases (SAPK) and may even inhibit ERK1 and ERK2 (29). Addition of exogenous ceramides or sphingomyelinase to cells induces SAPK-dependent transcriptional activity through activation of c-Jun. A dominant negative mutant of SEK1, the protein kinase that phosphorylates and activates SAPK, interferes with ceramide-induced apoptosis (30), which suggests that SAPK functions downstream of ceramide in the cell death pathway. The relation of SAPK to Rb and death proteases (such as prICE/CPP32) has not yet been determined.

Ceramide has an uncertain role in inducing the activity of NF-κB. TNF-α may induce activation of an acidic sphingomyelinase, and the resulting ceramide has been suggested to activate NF-κB (31). Exogenous ceramides have for the most part been shown not to induce nuclear translocation and activation of NF-κB (32). In the only studies to show such an effect, the degree of stimulation of NF-κB by ceramide was small relative to that observed with TNF-α (33). Also, ceramide appears not to induce transcription of NF-κB-dependent genes (29). Other studies have also dissociated the ceramide response from NF-κB activation (32, 34). For example, in cells treated with TNF-α, ceramide formation is not detected until after the induction of NF-κB. Treatment of cells with PDMP, which increases intracellular concentrations of ceramide, does not cause activation of NF-κB. Also, SR33557, an inhibitor of acid sphingomyelinase, does not inhibit TNF-induced activation of NF-κB. Finally, in Niemann-Pick fibroblast cells that lack acid sphingomyelinase, NF-κB is still activated in response to TNF-α and the effects of TNF-α on growth are preserved (35).

Ceramide may have a role in the regulation of protein secretion (36). Exogenously applied

C6-ceramide accumulates in the Golgi apparatus and interferes with the "constitutive" secretion of proteins, apolipoproteins, and triacylglycerol. The macrolide brefeldin A (BFA) induces sphingomyelin hydrolysis and mimics many of the cellular effects of exogenous ceramides, and exogenous ceramides bypass resistance to BFA. The effects of ceramide on protein secretion are opposed by okadaic acid and by phorbol ester activators of PKC, which suggests that protein secretion is under opposite regulation by modulators of protein kinases and phosphatases.

Other effects of ceramides include induction of differentiation of a number of cell types, including HL-60, glioma, and neuroblastoma cells (13, 37). Ceramide induces the transcription of cyclooxygenases 1 and 2 (COX) and αB-crystallin, a heat shock protein (13, 38). Ceramides have also been reported to inhibit esterification of cholesterol and to inhibit cytochrome P450 (39). In frog oocytes, ceramide triggers meiotic cell cycle progression (40).

Exogenous ceramides also stimulate the formation of prostaglandins and the release of IL-6 (41). The relative potency of various forms of ceramide in inducing these proinflammatory effects does not match that for the apoptotic effects (for example, D-*threo*-ceramide, which is an unnatural analog, is the most potent ceramide in inducing IL-6 secretion). This raises the possibility that molecules other than D-*erythro*-ceramide are the physiologic mediators of these effects.

Mechanisms of Ceramide Action

Biologically relevant and direct targets of ceramide should be activated by ceramide in vitro, and they should mediate the most proximal effects of ceramide in cells. There are three potential candidates for direct targets of ceramide action.

Ceramide-activated protein phosphatase (CAPP). In vitro, ceramide activates a serine-threonine protein phosphatase. This phosphatase is related to the PP2A family of phosphatases because it copurifies with the heterotrimeric form of PP2A and is inhibited potently by okadaic acid in vitro (42). It is also activated by ceramides with various N-linked acyl groups, but is not activated by other sphingolipids or neutral lipids. Studies in *S. cerevisiae* demonstrate that yeast CAPP is composed of the catalytic subunit encoded by *SIT4* and the regulatory subunits encoded by *CDC55* and *TPD3* (43).

Several lines of evidence suggest a role for CAPP in mediating at least some of the cellular activities of ceramide (21, 42, 43, 44). First, some of ceramide's effects on cells (such as apoptosis and down-regulation of the c-*myc* protooncogene) are inhibited by low concentrations of okadaic acid. Second, CAPP is activated in vitro by ceramide but not by dihydroceramide, which is inactive in eliciting ceramide effects on cells. Third, studies in *S. cerevisiae* show that yeast cells deficient in the various subunits of CAPP become resistant to the effects of ceramide. Further studies will be required to determine the relevant physiologic substrates for CAPP.

PKC ζ. Ceramide induces phosphorylation of PKC ζ in cells, and it activates the enzyme in vitro (45).

Ceramide-activated protein kinase (CAPK). CAPK is a membrane-associated kinase with a substrate specificity for serine or threonine in proximity to proline (46). Treatment of cells with sphingosine (but not C2-ceramide) results in a unique phosphorylation of Thr^{669} on the epidermal growth factor (EGF)

receptor, and C8-ceramide mimics the effects of sphingosine and EGF (47). In vitro, ceramide does not activate this kinase in a partially purified preparation, which raises the possibility that this kinase is not directly regulated by ceramide (48).

Regulation of Ceramide Formation

There are several possible sources of ceramide that accumulates in response to extracellular stimuli and agents of injury.

Sphingomyelinases. Current studies point to sphingomyelin as the major precursor for ceramide and to sphingomyelinase as the major enzyme responsible for ceramide generation. At least three distinct sphingomyelinases are implicated in distinct pathways. In HL-60 cells, 1,25-dihydroxyvitamin D_3 causes the activation of a Mg^{2+}-independent sphingomyelinase, which is active at neutral pH. This enzyme has been purified, and its cytosolic localization and Mg^{2+} independence distinguish it from the Mg^{2+}-dependent membrane sphingomyelinase (49).

A Mg^{2+}-dependent membrane neutral sphingomyelinase is activated in response to TNF-α or serum deprivation (14). The temporal profile of its activation coincides with the major and delayed phase of ceramide accumulation, which suggests that it may participate in mediating the apoptotic and antiproliferative activities of TNF-α, Fas, 1-β-D-arabinofuranosylcytosine (Ara C), and other inducers of apoptosis. In HL-60 cells, arachidonate causes accumulation of ceramide and activation of the Mg^{2+}-dependent sphingomyelinase in cell-free extracts (50). Because TNF-α activates phospholipase A2 (51), these studies may indicate that arachidonate (or one of its many products) is coupled to activation of neutral sphingomyelinase.

In addition, proteases are implicated in a pathway leading from TNF-α to the activation of sphingomyelinase (14, 52). Overexpression of CrmA (a viral protein that functions as a protease inhibitor with high affinity to ICE and related proteases) inhibits ceramide formation in response to TNF-α and protects cells from the cytotoxic action of TNF-α but not from that of ceramide. Reaper, a *Drosophila* gene product that causes cell death, results in ceramide formation that is abrogated by pharmacological inhibitors of ICE-like proteases. Acid sphingomyelinase has been proposed as a mediator of some of the activities of TNF-α, especially in the regulation of NF-κB (31) as discussed in the previous section.

De novo synthesis. The de novo synthesis of ceramide is stimulated by retinoic acid, by the exchange of medium in tissue culture, and by the chemotherapeutic agent daunorubicin (12, 53). However, daunorubicin induces a biphasic response in sphingomyelin hydrolysis and ceramide generation, and fumonisin B, an inhibitor of ceramide synthase, does not inhibit ceramide formation or apoptosis in response to daunorubicin (54).

Function of Ceramide as a Biostat

Unlike adenosine 3′,5′-monophosphate (cyclic AMP), IP_3, phosphatidylinositol-3,4,5-trisphosphate (PIP_3), and many of the eicosanoids, ceramide and DAG do not function solely in signal transduction.

They are critical components in the intermediary metabolism of sphingolipids and glycerophospholipids. Also, the most pronounced changes in the amounts of ceramide and DAG occur over longer time frames than those seen with cyclic AMP, IP_3, or PIP_3. Therefore, ceramide may function more as a component of a "biostat" that measures and initiates responses to cellular stress, much as a thermostat measures and regulates temperature. For example, cellular concentrations of ceramide are increased by systemic stress (such as caused by TNF) or cell injury (such as from heat or chemotherapeutic agents). The cell then responds to these changes by undergoing apoptosis or growth arrest.

This concept of lipid biostats also offers a solution to the paradoxical dual function of ceramide and DAG as intermediary metabolites as well as second messengers and bioeffector molecules. Multiple enzymes are capable of regulating ceramide concentrations through distinct metabolic pathways (Fig. 3), and these individual enzymes may be activated by distinct stresses or extracellular agents. These enzymes may then serve to integrate the effects of several stimuli as a consequence of the regulation of ceramide concentrations. The ceramide concentrations would then reflect the effects of several stimuli and would serve as a gauge of the overall amount of stress or injury to which the cell has been exposed.

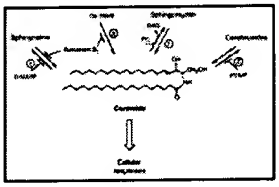

Fig. 3. Proposed role for ceramide and ceramide metabolism in the regulation of growth suppression. Ceramide plays a key role in sphingolipid metabolism, both as a key intermediate in sphingolipid metabolism and as a penultimate product in sphingolipid degradation. Various enzymes such as sphingomyelinases (1), de novo pathways of ceramide formation (3), cerebroside synthase (2), and ceramidase (4) may contribute to the regulation of ceramide concentrations. Therefore, it is proposed that various enzymes involved in ceramide metabolism can be potentially regulated in response to distinct classes of agents. The common effect of these pathways would be the accumulation of ceramide, which would then function as a biostat and launch various aspects of ceramide-mediated biology such as cell cycle arrest, cell senescence, or apoptosis.
[View Larger Version of this Image (13K GIF file)]

Studies of ceramide regulation and function, and more general studies of apoptosis and growth suppression, are beginning to define regulated pathways that ultimately function to deal with systemic as well as cellular stress and injury that may lead to cell cycle arrest, terminal differentiation, senescence, or apoptosis. Additional tools, such as inhibitors of specific enzymes of ceramide generation, are required to substantiate the hypotheses raised here. Understanding of these pathways may provide a basis for development of therapies to control cancer and inflammation.

REFERENCES AND NOTES

1. N. Divecha and R. F. Irvine, *Cell* **80**, 269 (1995) [Medline]; W. H. Moolenaar, *J. Biol. Chem.* **270**, 12949 (1995) [Medline]; M. Liscovitch and L. C. Cantley, *Cell* **77**, 329 (1994) [Medline]; J. H. Exton, *Biochim. Biophys. Acta Lipids Lipid Metab.* **1212**, 26 (1994); C. N. Serhan, *Biochim. Biophys. Acta* **1212**, 1 (1994) [Medline].

2. Y. A. Hannun and R. M. Bell, *Science* **243**, 500 (1989) [Medline].
3. R. O. Brady, in *The Metabolic Basis of Inherited Disease*, J. B. Stanbury, J. B. Wyngaarden, D. S. Fredrickson, J. L. Goldstein, M. S. Brown, Eds. (McGraw-Hill, New York, 1983), p. 831-841.
4. K. Hanada *et al.*, *J. Biol. Chem.* **267**, 23527 (1992); R. Buede, C. Rinker-Schaffer, W. J. Pinto, R. L. Lester, R. C. Dickson, *J. Bacteriol.* **173**, 4325 (1991) [Medline].
5. M. Tomita, R. Taguchi, H. Ikezawa, *J. Toxicol. Toxin Rev.* **10**, 169 (1991); E. Wang, W. P. Norred, C. W. Bacon, R. T. Riley, A. H. Merrill Jr., *J. Biol. Chem.* **266**, 14486 (1991) [Medline]; M. M. Zweerink, A. M. Edison, G. B. Wells, W. Pinto, R. L. Lester, *ibid.* **267**, 25032 (1992) [Medline]; O. D. Hensens, G. L. Helms, E. T. T. Jones, G. H. Harris, *J. Org. Chem.* **60**, 1772 (1995) .
6. A. H. Merrill Jr., *J. Bioenerg. Biomembr.* **23**, 83 (1991) [Medline]; Y. A. Hannun and C. M. Linardic, *Biochim. Biophys. Acta Bio-Membr.* **1154**, 223 (1993); S. Hakomori, *J. Biol. Chem.* **265**, 18713 (1990) [Medline]; S. Mathias and R. Kolesnick, *Adv. Lipid Res.* **25**, 65 (1993) [Medline]; S. Spiegel and S. Milstien, *J. Membr. Biol.* **146**, 225 (1995) [Medline]; M. Liscovitch and Y. Lavie, *Biochem. Pharmacol.* **42**, 2071 (1991) [Medline].
7. Y. A. Hannun, *J. Biol. Chem.* **269**, 3125 (1994) [Medline]; J. D. Saba, L. M. Obeid, Y. A. Hannun, *Philos. Trans. R. Soc. London Ser. B* **351**, 233 (1996) [Medline]; R. Kolesnick and D. W. Golde, *Cell* **77**, 325 (1994) [Medline].
8. P. P. Van Veldhoven, T. J. Matthews, D. P. Bolognesi, R. M. Bell, *Biochem. Biophys. Res. Commun.* **187**, 209 (1992) [Medline]; C. De Simone *et al.*, *Immunol. Today* **17**, 48 (1996).
9. M. E. Venable, J. Y. Lee, M. J. Smyth, A. Bielawska, L. M. Obeid, *J. Biol. Chem.* **270**, 30701 (1995) [Medline].
10. K. A. Dressler, S. Mathias, R. N. Kolesnick, *Science* **255**, 1715 (1992) [Medline]; A. Haimovitz-Friedman *et al.*, *J. Exp. Med.* **180**, 525 (1994); M. G. Cifone*et al.*, *ibid.*, p. 1547; S. Mathias *et al.*, *Science* **259**, 519 (1993).
11. M.-Y. Kim, C. Linardic, L. Obeid, Y. Hannun, *J. Biol. Chem.* **266**, 484 (1991) [Medline]; N. Andrieu, R. Salvayre, T. Levade, *Biochem. J.* **303**, 341 (1994) [Medline]; C. G. Tepper*et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 8443 (1995).
12. E. R. Smith and A. H. Merrill Jr., *J. Biol. Chem.* **270**, 18749 (1995) [Medline].
13. L. R. Ballou, C. P. Chao, M. A. Holness, S. C. Barker, R. Raghow, *ibid.* **267**, 20044 (1992) [Medline]; J. Q. Chen, M. Nikolova-Karakashian, A. H. Merrill Jr., E. T. Morgan, *ibid.* **270**, 25233 (1995) ; F. Yanaga and S. P. Watson, *Biochem. J.* **298**, 733 (1994) [Medline]; T. Okazaki, R. M. Bell, Y. A. Hannun, *J. Biol. Chem.* **264**, 19076 (1989) [Medline]; T. Okazaki, A. Bielawska, R. M. Bell, Y. A. Hannun, *ibid.* **265**, 15823 (1990) [Medline]; R. T. Dobrowsky, M. H. Werner, A. M. Castellino, M. V. Chao, Y. A. Hannun, *Science* **265**, 1596 (1994) [Medline]; R. T. Dobrowsky, G. M. Jenkins, Y. A. Hannun, *J. Biol. Chem.* **270**, 22135 (1995) [Medline].
14. S. Jayadev *et al.*, *J. Biol. Chem.* **270**, 2047 (1995); G. S. Dbaibo *et al.*, unpublished observations.
15. C. M. Linardic and Y. A. Hannun, *J. Biol. Chem.* **269**, 23530 (1994) [Medline]; N. Andrieu, R. Salvayre, T. Levade, *Eur. J. Biochem.* **236**, 738 (1996) [Medline].
16. P. S. Liu and R. G. W. Anderson, *J. Biol. Chem.* **270**, 27179 (1995) .
17. A. Bielawska, C. M. Linardic, Y. A. Hannun, *FEBS Lett.* **307**, 211 (1992) [Medline]; L. M. Obeid, C. M. Linardic, L. A. Karolak, Y. A. Hannun, *Science* **259**, 1769 (1993) [Medline]; W. D. Jarvis*et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **91**, 73 (1994).
18. A. Bielawska, H. M. Crane, D. Liotta, L. M. Obeid, Y. A. Hannun, *J. Biol. Chem.* **268**, 26226 (1993) [Medline].
19. L. Riboni, R. Bassi, S. Sonnino, G. Tettamanti, *FEBS Lett.* **300**, 188 (1992) [Medline]; A. H. Merrill Jr. *et al.*, *J. Biol. Chem.* **261**, 12610 (1986); A. H. Merrill Jr. and E. Wang, *Methods Enzymol.* **209**, 427 (1992) [Medline]; W. D. Jarvis, A. J. Turner, L. F. Povirk, R. S. Traylor, S. Grant, *Cancer Res.* **54**, 1707 (1994) [Medline]; C. S. S. Rani*et al.*, *J. Biol. Chem.* **270**, 2859 (1995); A. Bielawska *et al.*, *ibid.* **271**, 12646 (1996).

20. A. Gómez-Muñoz, D. W. Waggoner, L. O'Brien, D. N. Brindley, *J. Biol. Chem.* **270**, 26318 (1995) [Medline]; G. Dbaibo *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 1347 (1995).
21. R. A. Wolff, R. T. Dobrowsky, A. Bielawska, L. M. Obeid, Y. A. Hannun, *J. Biol. Chem.* **269**, 19605 (1994) [Medline].
22. A. Gómez-Muñoz, A. Martin, L. O'Brien, D. N. Brindley, *ibid.*, p. 8937; T. Nakamura *et al.*, *ibid.*, p. 18384; M. E. Venable, G. C. Blobe, L. M. Obeid, *ibid.*, p. 26040; Z. Kiss and E. Deli, *FEBS Lett.* **365**, 146 (1995) [Medline]; M. J. Jones and A. W. Murray, *J. Biol. Chem.* **270**, 5007 (1995) [Medline]; Y. Nakamura *et al.*, *J. Immunol.* **156**, 256 (1996); K. Wong, X.-B. Li, N. Hunchuk, *J. Biol. Chem.* **270**, 3056 (1995) [Medline].
23. J. Quintans, J. Kilkus, C. L. McShan, A. R. Gottschalk, G. Dawson, *Biochem. Biophys. Res. Commun.* **202**, 710 (1994) [Medline]; M. Chen *et al.*, *Cancer Res.* **55**, 991 (1995); S. J. Martin *et al.*, *EMBO J.* **14**, 5191 (1995); H. Sawai *et al.*, *J. Biol. Chem.* **270**, 27326 (1995); B. Brugg, P. P. Michel, Y. Agid, M. Ruberg, *J. Neurochem.* **66**, 733 (1996) [Medline].
24. M. J. Smyth *et al.*, *Biochem. J.* **316**, 25 (1996); S. J. Martin *et al.*, *J. Biol. Chem.* **270**, 6425 (1995).
25. J. Zhang *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **93**, 5325 (1996).
26. S. J. Martin *et al.*, *Cell Death Differ.* **2**, 253 (1995).
27. A. Ito and K. Horigome, *J. Neurochem.* **65**, 463 (1995) [Medline]; Y. Goodman and M. P. Mattson, *ibid.* **66**, 869 (1996) [Medline].
28. M. A. Raines, R. N. Kolesnick, D. W. Golde, *J. Biol. Chem.* **268**, 14572 (1993) [Medline].
29. J. K. Westwick, A. E. Bielawska, G. Dbaibo, Y. A. Hannun, D. A. Brenner, *ibid.* **270**, 22689 (1995) [Medline]; S. Pyne, J. Chapman, L. Steele, N. J. Pyne, *Eur. J. Biochem.* **237**, 819 (1996) [Medline]; K. M. Latinis and G. A. Koretzky, *Blood* **87**, 871 (1996) [Medline].
30. M. Verheij *et al.*, *Nature* **380**, 75 (1996).
31. S. Schütze, T. Machleidt, M. Krönke, *J. Leukocyte Biol.* **56**, 533 (1994) [Medline]; S. Schütze *et al.*, *Cell* **71**, 765 (1992).
32. G. Dbaibo, L. M. Obeid, Y. A. Hannun, *J. Biol. Chem.* **268**, 17762 (1993) [Medline]; J. C. Betts, A. B. Agranoff, G. J. Nabel, J. A. Shayman, *ibid.* **269**, 8455 (1994) [Medline].
33. Z. Yang, M. Costanzo, D. W. Golde, R. N. Kolesnick, *ibid.* **268**, 20520 (1993) [Medline]; S. A. G. Reddy *et al.*, *ibid.* **269**, 25369 (1994) .
34. J.-P. Jaffrézou *et al.*, *Biochim. Biophys. Acta Mol. Cell Res.* **1266**, 1 (1995); M. Higuchi, S. Singh, J. -P. Jaffrézou, B. B. Aggarwal, *J. Immunol.* **157**, 297 (1996) [Medline].
35. K. Kuno, K. Sukegawa, Y. Ishikawa, T. Orii, K. Matsushima, *Int. Immunol.* **6**, 1269 (1994) [Medline].
36. R. E. Pagano, M. A. Sepanski, O. C. Martin, *J. Cell Biol.* **109**, 2067 (1989) [Medline]; A. G. Rosenwald and R. E. Pagano, *J. Biol. Chem.* **268**, 4577 (1993) [Medline]; F. J. Field, H. Chen, E. Born, B. Dixon, S. Mathur, *J. Clin. Invest.* **92**, 2609 (1993) [Medline]; C. M. Linardic, S. Jayadev, Y. A. Hannun, *J. Biol. Chem.* **267**, 14909 (1992) [Medline]; T. Oda, C.-H. Chen, H. C. Wu, *ibid.* **270**, 4088 (1995) [Medline]; C. M. Linardic, S. Jayadev, Y. A. Hannun, *Cell Growth Differ.* **7**, 765 (1996) [Medline].
37. L. Riboni, A. Prinetti, R. Bassi, A. Caminiti, G. Tettamanti, *J. Biol. Chem.* **270**, 26868 (1995) [Medline].
38. M. Hayakawa, S. Jayadev, M. Tsujimoto, Y. A. Hannun, F. Ito, *Biochem. Biophys. Res. Commun.* **220**, 681 (1996) [Medline]; Y. Chang, A. Abe, J. A. Shayman, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 12275 (1995) [Medline].
39. N. D. Ridgway, *Biochim. Biophys. Acta Lipids Lipid Metab.* **1256**, 39 (1995); P. Santana *et al.*, *Endocrinology* **136**, 2345 (1995) [Medline].
40. J. C. Strum, K. I. Swenson, J. E. Turner, R. M. Bell, *J. Biol. Chem.* **270**, 13541 (1995) [Medline].
41. S. J. F. Laulederkind, A. Bielawska, R. Raghow, Y. A. Hannun, L. R. Ballou, *J. Exp. Med.* **182**, 599 (1995) .
42. R. T. Dobrowsky and Y. A. Hannun, *J. Biol. Chem.* **267**, 5048 (1992) [Medline]; R. T. Dobrowsky,

C. Kamibayashi, M. C. Mumby, Y. A. Hannun, *ibid.* **268**, 15523 (1993) [Medline]; B. Law and S. Rossie, *ibid.* **270**, 12808 (1995) [Medline]; R. T. Dobrowsky and Y. A. Hannun, *Adv. Lipid Res.* **25**, 91 (1993) [Medline].
43. J. T. Nickels and J. R. Broach, *Genes Dev.* **10**, 382 (1996) [Medline].
44. J. D. Fishbein, R. T. Dobrowsky, A. Bielawska, S. Garrett, Y. A. Hannun, *J. Biol. Chem.* **268**, 9255 (1993) [Medline].
45. G. Müller *et al.*, *EMBO J.* **14**, 1961 (1995) [Medline]; J. Lozano *et al.*, *J. Biol. Chem.* **269**, 19200 (1994).
46. C. K. Joseph, H.-S. Byun, R. Bittman, R. N. Kolesnick, *J. Biol. Chem.* **268**, 20002 (1993) [Medline]; S. Mathias, K. A. Dressler, R. N. Kolesnick, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 10009 (1991) [Medline].
47. M. Faucher, N. Girones, Y. A. Hannun, R. M. Bell, R. Davis, *J. Biol. Chem.* **263**, 5319 (1988) [Medline]; T. Goldkorn *et al.*, *ibid.* **266**, 16092 (1991) [Medline].
48. J. Liu, S. Mathias, Z. Yang, R. N. Kolesnick, *ibid.* **269**, 3047 (1994) [Medline].
49. T. Okazaki, A. Bielawska, N. Domae, R. M. Bell, Y. A. Hannun, *ibid.*, p. 4070; M. W. Spence, *Adv. Lipid Res.* **26**, 3 (1993) [Medline]; S. Chatterjee, *ibid.*, p. 25.
50. S. Jayadev, C. M. Linardic, Y. A. Hannun, *J. Biol. Chem.* **269**, 5757 (1994) [Medline].
51. J. W. Larrick and S. C. Wright, *FASEB J.* **4**, 3215 (1990) [Medline]; M. Hayakawa *et al.*, *J. Biol. Chem.* **268**, 11290 (1993).
52. G. J. Pronk, K. Ramer, P. Amiri, L. T. Williams, *Science* **271**, 808 (1996) [Medline].
53. A. Kalén, R. A. Borchardt, R. M. Bell, *Biochim. Biophys. Acta Lipids Lipid Metab.* **1125**, 90 (1992); R. Bose*et al.*, *Cell* **82**, 405 (1995).
54. J.-P. Jaffrézou *et al.*, *EMBO J.* **15**, 2417 (1996).
55. G. Dbaibo, M. Pushkareva, N. Alter, M. Smyth, L. Obeid, Y. Hannun, unpublished observations.
56. Supported by NIH (grant GM43825), the U.S. Department of Defense (DAMD17-94J4301), and the American Cancer Society (CB122). I thank L. Obeid for a careful and critical review of the manuscript.

- **Abstract** of this Article
- Similar articles found in: SCIENCE Online PubMed
- PubMed Citation
- This Article has been cited by:
- Search Medline for articles by: Hannun, Y. A.
- Alert me when: new articles cite this article
- Download to Citation Manager

- Collections under which this article appears: **Cell Biology**

This article has been cited by other articles:

- Boland, M. P., Foster, S. J., O'Neill, L. A. J. (1997). Daunorubicin Activates NFkappa B and Induces kappa B-dependent Gene Expression in HL-60 Promyelocytic and Jurkat T Lymphoma Cells. *J. Biol. Chem.* 272: 12952-12960 [Abstract] [Full Text]
- Exton, J. H. (1997). New Developments in Phospholipase D. *J. Biol. Chem.* 272: 15579-15582 [Full Text]
- Watts, J. D., Gu, M., Polverino, A. J., Patterson, S. D., Aebersold, R. (1997). Fas-induced apoptosis of T cells occurs independently of ceramide generation. *Proc. Natl. Acad. Sci. U. S. A.* 94: 7292-7296 [Abstract] [Full Text]
- Edsall, L. C., Pirianov, G. G., Spiegel, S. (1997). Involvement of Sphingosine 1-Phosphate in Nerve Growth Factor-Mediated Neuronal Survival and Differentiation. *J. Neurosci.* 17: 6952-6960 [Abstract] [Full Text]
- Dickson, R. C., Nagiec, E. E., Skrzypek, M., Tillman, P., Wells, G. B., Lester, R. L. (1997). Sphingolipids Are Potential Heat Stress Signals in Saccharomyces. *J. Biol. Chem.* 272: 30196-30200 [Abstract] [Full Text]
- Haimovitz-Friedman, A., Cordon-Cardo, C., Bayoumy, S., Garzotto, M., McLoughlin, M., Gallily, R., Edwards, C. K. III, Schuchman, E. H., Fuks, Z., Kolesnick, R. (1997). Lipopolysaccharide Induces Disseminated Endothelial Apoptosis Requiring Ceramide Generation. *J. Exp. Med.* 186: 1831-1841 [Abstract] [Full Text]
- Sontag, E., Sontag, J.-M., Garcia, A. (1997). Protein phosphatase 2A is a critical regulator of protein kinase C zeta signaling targeted by SV40 small t to promote cell growth and NF-kappa B activation. *EMBO J.* 16: 5662-5671 [Abstract] [Full Text]
- Mandala, S. M., Thornton, R. A., Rosenbach, M., Milligan, J., Garcia-Calvo, M., Bull, H. G., Kurtz, M. B. (1997). Khafrefungin, a Novel Inhibitor of Sphingolipid Synthesis. *J. Biol. Chem.* 272: 32709-32714 [Abstract] [Full Text]
- Marathe, S., Schissel, S. L., Yellin, M. J., Beatini, N., Mintzer, R., Williams, K. J., Tabas, I.

(1998). Human Vascular Endothelial Cells Are a Rich and Regulatable Source of Secretory Sphingomyelinase. IMPLICATIONS FOR EARLY ATHEROGENESIS AND CERAMIDE-MEDIATED CELL SIGNALING. *J. Biol. Chem.* 273: 4081-4088 [Abstract] [Full Text]

- Amarante-Mendes, G. P., Naekyung Kim, C., Liu, L., Huang, Y., Perkins, C. L., Green, D. R., Bhalla, K. (1998). Bcr-Abl Exerts Its Antiapoptotic Effect Against Diverse Apoptotic Stimuli Through Blockage of Mitochondrial Release of Cytochrome C and Activation of Caspase-3. *Blood* 91: 1700-1705 [Abstract] [Full Text]
- Harada-Shiba, M., Kinoshita, M., Kamido, H., Shimokado, K. (1998). Oxidized Low Density Lipoprotein Induces Apoptosis in Cultured Human Umbilical Vein Endothelial Cells by Common and Unique Mechanisms. *J. Biol. Chem.* 273: 9681-9687 [Abstract] [Full Text]
- Grilley, M. M., Stock, S. D., Dickson, R. C., Lester, R. L., Takemoto, J. Y. (1998). Syringomycin Action Gene SYR2 Is Essential for Sphingolipid 4-Hydroxylation in Saccharomyces cerevisiae. *J. Biol. Chem.* 273: 11062-11068 [Abstract] [Full Text]
- Olivera, A., Kohama, T., Tu, Z., Milstien, S., Spiegel, S. (1998). Purification and Characterization of Rat Kidney Sphingosine Kinase. *J. Biol. Chem.* 273: 12576-12583 [Abstract] [Full Text]
- Mandala, S. M., Thornton, R. A., Milligan, J., Rosenbach, M., Garcia-Calvo, M., Bull, H. G., Harris, G., Abruzzo, G. K., Flattery, A. M., Gill, C. J., Bartizal, K., Dreikorn, S., Kurtz, M. B. (1998). Rustmicin, a Potent Antifungal Agent, Inhibits Sphingolipid Synthesis at Inositol Phosphoceramide Synthase. *J. Biol. Chem.* 273: 14942-14949 [Abstract] [Full Text]
- Ruiz-Arguello, M. B., Goni, F. M., Alonso, A. (1998). Vesicle Membrane Fusion Induced by the Concerted Activities of Sphingomyelinase and Phospholipase C. *J. Biol. Chem.* 273: 22977-22982 [Abstract] [Full Text]
- van Echten-Deckert, G., Schick, A., Heinemann, T., Schnieders, B. (1998). Phosphorylated cis-4-Methylsphingosine Mimics the Mitogenic Effect of Sphingosine-1-phosphate in Swiss 3T3 Fibroblasts. *J. Biol. Chem.* 273: 23585-23589 [Abstract] [Full Text]
- Brindley, D. N., Waggoner, D. W. (1998). Mammalian Lipid Phosphate Phosphohydrolases. *J. Biol. Chem.* 273: 24281-24284 [Full Text]
- Mathes, C., Fleig, A., Penner, R. (1998). Calcium Release-activated Calcium Current (ICRAC) Is a Direct Target for Sphingosine. *J. Biol. Chem.* 273: 25020-25030 [Abstract] [Full Text]
- Takehara, T., Hayashi, N., Mita, E., Kanto, T., Tatsumi, T., Sasaki, Y., Kasahara, A., Hori, M. (1998). Delayed Fas-Mediated Hepatocyte Apoptosis During Liver Regeneration in Mice: Hepatoprotective Role of TNFalpha. *Hepatology* 27: 1643-1651 [Abstract] [Full Text]
- Chujor, C. S. N., Feingold, K. R., Elias, P. M., Holleran, W. M. (1998). Glucosylceramide synthase activity in murine epidermis: quantitation, localization, regulation, and requirement for barrier homeostasis. *J. Lipid Res.* 39: 277-285 [Abstract] [Full Text]
- Escargueil-Blanc, I., Andrieu-Abadie, N., Caspar-Bauguil, S., Brossmer, R., Levade, T., Negre-Salvayre, A., Salvayre, R. (1998). Apoptosis and Activation of the Sphingomyelin-Ceramide Pathway Induced by Oxidized Low Density Lipoproteins Are Not Causally Related in ECV-304 Endothelial Cells. *J. Biol. Chem.* 273: 27389-27395 [Abstract] [Full Text]
- Farrell, A. M., Uchida, Y., Nagiec, M. M., Harris, I. R., Dickson, R. C., Elias, P. M., Holleran, W. M. (1998). UVB irradiation up-regulates serine palmitoyltransferase in cultured human keratinocytes. *J. Lipid Res.* 39: 2031-2038 [Abstract] [Full Text]
- Yano, M., Kishida, E., Muneyuki, Y., Masuzawa, Y. (1998). Quantitative analysis of ceramide molecular species by high performance liquid chromatography. *J. Lipid Res.* 39: 2091-2098 [Abstract] [Full Text]
- Liu, B., Hassler, D. F., Smith, G. K., Weaver, K., Hannun, Y. A. (1998). Purification and Characterization of a Membrane Bound Neutral pH Optimum Magnesium-dependent and Phosphatidylserine-stimulated Sphingomyelinase from Rat Brain. *J. Biol. Chem.* 273:

34472-34479 [Abstract] [Full Text]
- MacKichan, M. L., DeFranco, A. L. (1999). Role of Ceramide in Lipopolysaccharide (LPS)-induced Signaling. LPS INCREASES CERAMIDE RATHER THAN ACTING AS A STRUCTURAL HOMOLOG. *J. Biol. Chem.* 274: 1767-1775 [Abstract] [Full Text]
- Bettaïeb, A., Plo, I., Mansat-De Mas, V., Quillet-Mary, A., Levade, T., Laurent, G., Jaffrézou, J.-P. (1999). Daunorubicin- and Mitoxantrone-Triggered Phosphatidylcholine Hydrolysis: Implication in Drug-Induced Ceramide Generation and Apoptosis. *Mol Pharmacol* 55: 118-125 [Abstract] [Full Text]
- Doi, T. S., Marino, M. W., Takahashi, T., Yoshida, T., Sakakura, T., Old, L. J., Obata, Y. (1999). Absence of tumor necrosis factor rescues RelA-deficient mice from embryonic lethality. *Proc. Natl. Acad. Sci. U. S. A.* 96: 2994-2999 [Abstract] [Full Text]
- Komori, H., Ichikawa, S., Hirabayashi, Y., Ito, M. (1999). Regulation of Intracellular Ceramide Content in B16 Melanoma Cells. BIOLOGICAL IMPLICATIONS OF CERAMIDE GLYCOSYLATION. *J. Biol. Chem.* 274: 8981-8987 [Abstract] [Full Text]
- Karasawa, K., Qiu, X., Lee, T.-c. (1999). Purification and Characterization from Rat Kidney Membranes of a Novel Platelet-activating Factor (PAF)-dependent Transacetylase That Catalyzes the Hydrolysis of PAF, Formation of PAF Analogs, and C2-ceramide. *J. Biol. Chem.* 274: 8655-8661 [Abstract] [Full Text]
- Cifone, M. G., Migliorati, G., Parroni, R., Marchetti, C., Millimaggi, D., Santoni, A., Riccardi, C. (1999). Dexamethasone-Induced Thymocyte Apoptosis: Apoptotic Signal Involves the Sequential Activation of Phosphoinositide-Specific Phospholipase C, Acidic Sphingomyelinase, and Caspases. *Blood* 93: 2282-2296 [Abstract] [Full Text]
- Medvedev, A. E., Blanco, J. C. G., Qureshi, N., Vogel, S. N. (1999). Limited Role of Ceramide in Lipopolysaccharide-mediated Mitogen-activated Protein Kinase Activation, Transcription Factor Induction, and Cytokine Release. *J. Biol. Chem.* 274: 9342-9350 [Abstract] [Full Text]
- Zundel, W., Giaccia, A. (1998). Inhibition of the anti-apoptotic PI(3)K/Akt/Bad pathway by stress. *Genes & Dev.* 12: 1941-1946 [Abstract] [Full Text]
- Lehtonen, J. Y. A., Horiuchi, M., Daviet, L., Akishita, M., Dzau, V. J. (1999). Activation of the de novo Biosynthesis of Sphingolipids Mediates Angiotensin II Type 2 Receptor-induced Apoptosis. *J. Biol. Chem.* 274: 16901-16906 [Abstract] [Full Text]
- Memon, R. A., Holleran, W. M., Moser, A. H., Seki, T., Uchida, Y., Fuller, J., Shigenaga, J. K., Grunfeld, C., Feingold, K. R. (1998). Endotoxin and Cytokines Increase Hepatic Sphingolipid Biosynthesis and Produce Lipoproteins Enriched in Ceramides and Sphingomyelin. *Arterioscler Thromb* 18: 1257-1265 [Abstract] [Full Text]
- Hisano, N., Yatomi, Y., Satoh, K., Akimoto, S., Mitsumata, M., Fujino, M. A., Ozaki, Y. (1999). Induction and Suppression of Endothelial Cell Apoptosis by Sphingolipids: A Possible In Vitro Model for Cell-Cell Interactions Between Platelets and Endothelial Cells. *Blood* 93: 4293-4299 [Abstract] [Full Text]
- Jones, B. E., Lo, C. R., Srinivasan, A., Valentino, K. L., Czaja, M. J. (1999). Ceramide Induces Caspase-Independent Apoptosis in Rat Hepatocytes Sensitized by Inhibition of RNA Synthesis. *Hepatology* 30: 215-222 [Abstract] [Full Text]
- ANDRIEU-ABADIE, N., JAFFRÉZOU, J.-P., HATEM, S., LAURENT, G., LEVADE, T., MERCADIER, J.-J. (1999). L-carnitine prevents doxorubicin-induced apoptosis of cardiac myocytes: role of inhibition of ceramide generation. *FASEB J.* 13: 1501-1510 [Abstract] [Full Text]
- Dickson, R. C. (1998). SPHINGOLIPID FUNCTIONS IN SACCHAROMYCES CEREVISIAE: Comparison to Mammals. *Annu. Rev. Biochem.* 67: 27-48 [Abstract] [Full Text]
- Li, A. E., Ito, H., Rovira, I. I., Kim, K.-S., Takeda, K., Yu, Z.-Y., Ferrans, V. J., Finkel, T. (1999). A Role for Reactive Oxygen Species in Endothelial Cell Anoikis. *Circulation Research* 85: 304-310 [Abstract] [Full Text]

- Sol, N., Le Junter, J., Vassias, I., Freyssinier, J. M., Thomas, A., Prigent, A. F., Rudkin, B. B., Fichelson, S., Morinet, F. (1999). Possible Interactions between the NS-1 Protein and Tumor Necrosis Factor Alpha Pathways in Erythroid Cell Apoptosis Induced by Human Parvovirus B19. *J. Virol.* 73: 8762-8770 [Abstract] [Full Text]
- Thomas, R. L. Jr., Matsko, C. M., Lotze, M. T., Amoscato, A. A. (1999). Mass Spectrometric Identification of Increased C16 Ceramide Levels During Apoptosis. *J. Biol. Chem.* 274: 30580-30588 [Abstract] [Full Text]
- Mas, V. M.-D., Bezombes, C., Quillet-Mary, A., Bettaïeb, A., D'orgeix, A. D. T., Laurent, G., Jaffrézou, J.-P. (1999). Implication of Radical Oxygen Species in Ceramide Generation, c-Jun N-Terminal Kinase Activation and Apoptosis Induced by Daunorubicin. *Mol Pharmacol* 56: 867-874 [Abstract] [Full Text]
- Obara, Y., Takahashi, M., Nakahata, N., Ohizumi, Y. (1999). Maitotoxin-induced nerve growth factor production accompanied by the activation of a voltage-insensitive Ca2+ channel in C6-BU-1 glioma cells. *Br. J. Pharmacol.* 127: 1577-1582 [Abstract] [Full Text]
- Marathe, S., Kuriakose, G., Williams, K. J., Tabas, I. (1999). Sphingomyelinase, an Enzyme Implicated in Atherogenesis, Is Present in Atherosclerotic Lesions and Binds to Specific Components of the Subendothelial Extracellular Matrix. *Arterioscler Thromb* 19: 2648-2658 [Abstract] [Full Text]
- Navas, T. A., Baldwin, D. T., Stewart, T. A. (1999). RIP2 Is a Raf1-activated Mitogen-activated Protein Kinase Kinase. *J. Biol. Chem.* 274: 33684-33690 [Abstract] [Full Text]
- Xia, P., Wang, L., Gamble, J. R., Vadas, M. A. (1999). Activation of Sphingosine Kinase by Tumor Necrosis Factor-alpha Inhibits Apoptosis in Human Endothelial Cells. *J. Biol. Chem.* 274: 34499-34505 [Abstract] [Full Text]
- Lepple-Wienhues, A., Belka, C., Laun, T., Jekle, A., Walter, B., Wieland, U., Welz, M., Heil, L., Kun, J., Busch, G., Weller, M., Bamberg, M., Gulbins, E., Lang, F. (1999). Stimulation of CD95 (Fas) blocks T lymphocyte calcium channels through sphingomyelinase and sphingolipids. *Proc. Natl. Acad. Sci. U. S. A.* 96: 13795-13800 [Abstract] [Full Text]
- Kwak, E., Gerald, N., Larochelle, D. A., Vithalani, K. K., Niswonger, M. L., Maready, M., De Lozanne, A. (1999). LvsA, a Protein Related to the Mouse Beige Protein, Is Required for Cytokinesis in Dictyostelium. *Mol. Biol. Cell* 10: 4429-4439 [Abstract] [Full Text]
- SCHIAVONE, N., ROSINI, P., QUATTRONE, A., DONNINI, M., LAPUCCI, A., CITTI, L., BEVILACQUA, A., NICOLIN, A., CAPACCIOLI, S. (2000). A conserved AU-rich element in the 3' untranslated region of bcl-2 mRNA is endowed with a destabilizing function that is involved in bcl-2 down-regulation during apoptosis. *FASEB J.* 14: 174-184 [Abstract] [Full Text]
- Tomiuk, S., Zumbansen, M., Stoffel, W. (2000). Characterization and Subcellular Localization of Murine and Human Magnesium-dependent Neutral Sphingomyelinase. *J. Biol. Chem.* 275: 5710-5717 [Abstract] [Full Text]
- Grullich, C., Sullards, M. C., Fuks, Z., Merrill, A. H. Jr., Kolesnick, R. (2000). CD95(Fas/APO-1) Signals Ceramide Generation Independent of the Effector Stage of Apoptosis. *J. Biol. Chem.* 275: 8650-8656 [Abstract] [Full Text]
- Mao, C., Xu, R., Bielawska, A., Obeid, L. M. (2000). Cloning of an Alkaline Ceramidase from Saccharomyces cerevisiae. AN ENZYME WITH REVERSE (CoA-INDEPENDENT) CERAMIDE SYNTHASE ACTIVITY. *J. Biol. Chem.* 275: 6876-6884 [Abstract] [Full Text]
- Burow, M. E., Weldon, C. B., Collins-Burow, B. M., Ramsey, N., McKee, A., Klippel, A., McLachlan, J. A., Clejan, S., Beckman, B. S. (2000). Cross-talk between Phosphatidylinositol 3-Kinase and Sphingomyelinase Pathways as a Mechanism for Cell Survival/Death Decisions. *J. Biol. Chem.* 275: 9628-9635 [Abstract] [Full Text]
- Chan, C., Goldkorn, T. (2000). Ceramide Path in Human Lung Cell Death. *Am J Respir Cell Mol Biol* 22: 460-468 [Abstract] [Full Text]
- Kiryu-Seo, S., Sasaki, M., Yokohama, H., Nakagomi, S., Hirayama, T., Aoki, S., Wada, K.,

Kiyama, H. (2000). Damage-induced neuronal endopeptidase (DINE) is a unique metallopeptidase expressed in response to neuronal damage and activates superoxide scavengers. *Proc. Natl. Acad. Sci. U. S. A.* 10.1073/pnas.070509897 [Abstract] [Full Text]

- Kiryu-Seo, S., Sasaki, M., Yokohama, H., Nakagomi, S., Hirayama, T., Aoki, S., Wada, K., Kiyama, H. (2000). Damage-induced neuronal endopeptidase (DINE) is a unique metallopeptidase expressed in response to neuronal damage and activates superoxide scavengers. *Proc. Natl. Acad. Sci. U. S. A.* 97: 4345-4350 [Abstract] [Full Text]
- van der Houven van Oordt, W., Diaz-Meco, M. T., Lozano, J., Krainer, A. R., Moscat, J., Cáceres, J. F. (2000). The MKK3/6-p38-signaling Cascade Alters the Subcellular Distribution of hnRNP A1 and Modulates Alternative Splicing Regulation. *J. Cell Biol.* 149: 307-316 [Abstract] [Full Text]
- Zheng, T., Li, W., Wang, J., Altura, B. T., Altura, B. M. (2000). Sphingomyelinase and ceramide analogs induce contraction and rises in [Ca2+]i in canine cerebral vascular muscle. *Am. J. Physiol.* 278: 1421H-1428 [Abstract] [Full Text]
- Wells, G. B., Dickson, R. C., Lester, R. L. (1998). Heat-induced Elevation of Ceramide in Saccharomyces cerevisiae via de Novo Synthesis. *J. Biol. Chem.* 273: 7235-7243 [Abstract] [Full Text]
- Ridgway, N. D., Lagace, T. A., Cook, H. W., Byers, D. M. (1998). Differential Effects of Sphingomyelin Hydrolysis and Cholesterol Transport on Oxysterol-binding Protein Phosphorylation and Golgi Localization. *J. Biol. Chem.* 273: 31621-31628 [Abstract] [Full Text]
- Brenner, B., Koppenhoefer, U., Weinstock, C., Linderkamp, O., Lang, F., Gulbins, E. (1997). Fas- or Ceramide-induced Apoptosis Is Mediated by a Rac1-regulated Activation of Jun N-terminal Kinase/p38 Kinases and GADD153. *J. Biol. Chem.* 272: 22173-22181 [Abstract] [Full Text]
- Emkey, R., Kahn, C. R. (1997). Cross-talk between Phorbol Ester-mediated Signaling and Tyrosine Kinase Proto-oncogenes. II COMPARISON OF PHORBOL ESTER AND SPHINGOMYELINASE-INDUCED PHOSPHORYLATION OF ErbB2 AND ErbB3. *J. Biol. Chem.* 272: 31182-31189 [Abstract] [Full Text]
- Hanada, K., Hara, T., Nishijima, M., Kuge, O., Dickson, R. C., Nagiec, M. M. (1997). A Mammalian Homolog of the Yeast LCB1 Encodes a Component of Serine Palmitoyltransferase, the Enzyme Catalyzing the First Step in Sphingolipid Synthesis. *J. Biol. Chem.* 272: 32108-32114 [Abstract] [Full Text]
- Jenkins, G. M., Richards, A., Wahl, T., Mao, C., Obeid, L., Hannun, Y. (1997). Involvement of Yeast Sphingolipids in the Heat Stress Response of Saccharomyces cerevisiae. *J. Biol. Chem.* 272: 32566-32572 [Abstract] [Full Text]
- Schissel, S. L., Jiang, X.-c., Tweedie-Hardman, J., Jeong, T.-s., Camejo, E. H., Najib, J., Rapp, J. H., Williams, K. J., Tabas, I. (1998). Secretory Sphingomyelinase, a Product of the Acid Sphingomyelinase Gene, Can Hydrolyze Atherogenic Lipoproteins at Neutral pH. IMPLICATIONS FOR ATHEROSCLEROTIC LESION DEVELOPMENT. *J. Biol. Chem.* 273: 2738-2746 [Abstract] [Full Text]
- Reiners, J. J. Jr., Clift, R. E. (1999). Aryl Hydrocarbon Receptor Regulation of Ceramide-induced Apoptosis in Murine Hepatoma 1c1c7 Cells. A FUNCTION INDEPENDENT OF ARYL HYDROCARBON RECEPTOR NUCLEAR TRANSLOCATOR. *J. Biol. Chem.* 274: 2502-2510 [Abstract] [Full Text]
- Sawai, H., Domae, N., Nagan, N., Hannun, Y. A. (1999). Function of the Cloned Putative Neutral Sphingomyelinase as Lyso-platelet Activating Factor-Phospholipase C. *J. Biol. Chem.* 274: 38131-38139 [Abstract] [Full Text]
- Yen, C.-l. E., Mar, M.-h., Zeisel, S. H. (1999). Choline deficiency-induced apoptosis in PC12 cells is associated with diminished membrane phosphatidylcholine and sphingomyelin, accumulation of ceramide and diacylglycerol, and activation of a caspase. *FASEB J.* 13: 135-142 [Abstract] [Full Text]
- Stock, S. D., Hama, H., Radding, J. A., Young, D. A., Takemoto, J. Y. (2000). Syringomycin E

Inhibition of Saccharomyces cerevisiae: Requirement for Biosynthesis of Sphingolipids with Very-Long-Chain Fatty Acids and Mannose- and Phosphoinositol-Containing Head Groups. *Antimicrob. Agents Chemother.* 44: 1174-1180 [Abstract] [Full Text]

- Pfeilschifter, J., Huwiler, A. (2000). Ceramides as Key Players in Cellular Stress Response. *News Physiol Sci* 15: 11-15 [Abstract] [Full Text]
- Holopainen, J. M., Lemmich, J., Richter, F., Mouritsen, O. G., Rapp, G., Kinnunen, P. K. J. (2000). Dimyristoylphosphatidylcholine/C16:0-Ceramide Binary Liposomes Studied by Differential Scanning Calorimetry and Wide- and Small-Angle X-Ray Scattering. *Biophys J* 78: 2459-2469 [Abstract] [Full Text]
- Manna, S. K., Sah, N. K., Aggarwal, B. B. (2000). Protein Tyrosine Kinase p56lck Is Required for Ceramide-induced but Not Tumor Necrosis Factor-induced Activation of NF-kappa B, AP-1, JNK, and Apoptosis. *J. Biol. Chem.* 275: 13297-13306 [Abstract] [Full Text]
- Sun, Y., Taniguchi, R., Tanoue, D., Yamaji, T., Takematsu, H., Mori, K., Fujita, T., Kawasaki, T., Kozutsumi, Y. (2000). Sli2 (Ypk1), a Homologue of Mammalian Protein Kinase SGK, Is a Downstream Kinase in the Sphingolipid-Mediated Signaling Pathway of Yeast. *Mol. Cell. Biol.* 20: 4411-4419 [Abstract] [Full Text]
- Hofmann, K., Tomiuk, S., Wolff, G., Stoffel, W. (2000). Cloning and characterization of the mammalian brain-specific, Mg2+-dependent neutral sphingomyelinase. *Proc. Natl. Acad. Sci. U. S. A.* 97: 5895-5900 [Abstract] [Full Text]
- Chung, N., Jenkins, G., Hannun, Y. A., Heitman, J., Obeid, L. M. (2000). Sphingolipids Signal Heat Stress-induced Ubiquitin-dependent Proteolysis. *J. Biol. Chem.* 275: 17229-17232 [Abstract] [Full Text]
- Mandala, S. M., Thornton, R., Galve-Roperh, I., Poulton, S., Peterson, C., Olivera, A., Bergstrom, J., Kurtz, M. B., Spiegel, S. (2000). Molecular cloning and characterization of a lipid phosphohydrolase that degrades sphingosine-1- phosphate and induces cell death. *Proc. Natl. Acad. Sci. U. S. A.* 10.1073/pnas.120146897v1 [Abstract] [Full Text]
- Blázquez, C., Sánchez, C., Daza, A., Galve-Roperh, I., Guzmán, M. (1999). The Stimulation of Ketogenesis by Cannabinoids in Cultured Astrocytes Defines Carnitine Palmitoyltransferase I as a New Ceramide-Activated Enzyme. *J Neurochem* 72: 1759-1768 [Abstract] [Full Text]
- Pahan, K., Dobashi, K., Ghosh, B., Singh, I. (1999). Induction of the Manganese Superoxide Dismutase Gene by Sphingomyelinase and Ceramide. *J Neurochem* 73: 513-520 [Abstract] [Full Text]
- Yoshimura, S.-i., Banno, Y., Nakashima, S., Hayashi, K., Yamakawa, H., Sawada, M., Sakai, N., Nozawa, Y. (1999). Inhibition of Neutral Sphingomyelinase Activation and Ceramide Formation by Glutathione in Hypoxic PC12 Cell Death. *J Neurochem* 73: 675-683 [Abstract] [Full Text]
- Yu, S. P., Yeh, C.-H., Gottron, F., Wang, X., Grabb, M. C., Choi, D. W. (1999). Role of the Outward Delayed Rectifier K+ Current in Ceramide-Induced Caspase Activation and Apoptosis in Cultured Cortical Neurons. *J Neurochem* 73: 933-941 [Abstract] [Full Text]
- Owada, K., Sanjo, N., Kobayashi, T., Mizusawa, H., Muramatsu, H., Muramatsu, T., Michikawa, M. (1999). Midkine Inhibits Caspase-Dependent Apoptosis via the Activation of Mitogen-Activated Protein Kinase and Phosphatidylinositol 3-Kinase in Cultured Neurons. *J Neurochem* 73: 2084-2092 [Abstract] [Full Text]
- Tepper, A. D., Ruurs, P., Wiedmer, T., Sims, P. J., Borst, J., van Blitterswijk, W. J. (2000). Sphingomyelin Hydrolysis to Ceramide during the Execution Phase of Apoptosis Results from Phospholipid Scrambling and Alters Cell-surface Morphology. *J. Cell Biol.* 150: 155-164 [Abstract] [Full Text]
- Shimizu, H., Banno, Y., Sumi, N., Naganawa, T., Kitajima, Y., Nozawa, Y. (1999). Activation of p38 Mitogen-Activated Protein Kinase and Caspases in UVB-Induced Apoptosis of Human Keratinocyte HaCaT Cells. *J Invest Dermatol* 112: 769-774 [Abstract] [Full Text]
- Buisson-Legendre, N., Emonard, H., Bernard, P., Hornebeck, W. (2000). Relationship Between

Cell-Associated Matrix Metalloproteinase 9 and Psoriatic Keratinocyte Growth. *J Invest Dermatol* 115: 213-218 [Abstract] [Full Text]

- Strelow, A., Bernardo, K., Adam-Klages, S., Linke, T., Sandhoff, K., Krönke, M., Adam, D. (2000). Overexpression of Acid Ceramidase Protects from Tumor Necrosis Factor-induced Cell Death. *J. Exp. Med.* 192: 601-612 [Abstract] [Full Text]
- Carlson, N. G., Wieggel, W. A., Chen, J., Bacchi, A., Rogers, S. W., Gahring, L. C. (1999). Inflammatory Cytokines IL-1{alpha}, IL-1{beta}, IL-6, and TNF-{alpha} Impart Neuroprotection to an Excitotoxin Through Distinct Pathways. *The JI* 163: 3963-3968 [Abstract] [Full Text]
- Simarro, M., Calvo, J., Vila, J. M., Places, L., Padilla, O., Alberola-Ila, J., Vives, J., Lozano, F. (1999). Signaling Through CD5 Involves Acidic Sphingomyelinase, Protein Kinase C-{zeta}, Mitogen-Activated Protein Kinase Kinase, and c-Jun NH2-Terminal Kinase. *The JI* 162: 5149-5155 [Abstract] [Full Text]
- Kirkham, P. A., Takamatsu, H.-H., Lam, E. W.-F., Parkhouse, R. M. E. (2000). Ligation of the WC1 Receptor Induces {gamma}{delta} T Cell Growth Arrest Through Fumonisin B1-Sensitive Increases in Cellular Ceramide. *The JI* 165: 3564-3570 [Abstract] [Full Text]
- Macfarlane, D. E., Manzel, L. (1998). Antagonism of Immunostimulatory CpG-Oligodeoxynucleotides by Quinacrine, Chloroquine, and Structurally Related Compounds. *The JI* 160: 1122-1131 [Abstract] [Full Text]
- Rudel, T., Zenke, F. T., Chuang, T.-H., Bokoch, G. M. (1998). Cutting Edge: p21-Activated Kinase (PAK) Is Required for Fas-Induced JNK Activation in Jurkat Cells. *The JI* 160: 7-11 [Abstract] [Full Text]
- Herget, T., Esdar, C., Oehrlein, S. A., Heinrich, M., Schutze, S., Maelicke, A., van Echten-Deckert, G. (2000). Production of Ceramides Causes Apoptosis during Early Neural Differentiation in Vitro. *J. Biol. Chem.* 275: 30344-30354 [Abstract] [Full Text]
- Klapisz, E., Masliah, J., Bérézíat, G., Wolf, C., Koumanov, K. S. (2000). Sphingolipids and cholesterol modulate membrane susceptibility to cytosolic phospholipase A2. *J. Lipid Res.* 41: 1680-1688 [Abstract] [Full Text]
- Ye, P., D'Ercole, A. J. (1999). Insulin-Like Growth Factor I Protects Oligodendrocytes from Tumor Necrosis Factor-{alpha}-Induced Injury. *Endocrinology* 140: 3063-3072 [Abstract] [Full Text]
- Tepper, A. D., Diks, S. H., van Blitterswijk, W. J., Borst, J. (2000). Glucosylceramide Synthase Does Not Attenuate the Ceramide Pool Accumulating during Apoptosis Induced by CD95 or Anti-cancer Regimens. *J. Biol. Chem.* 275: 34810-34817 [Abstract] [Full Text]
- Grether-Beck, S., Bonizzi, G., Schmitt-Brenden, H., Felsner, I., Timmer, A., Sies, H., Johnson, J. P., Piette, J., Krutmann, J. (2000). Non-enzymatic triggering of the ceramide signalling cascade by solar UVA radiation. *EMBO J.* 19: 5793-5800 [Abstract] [Full Text]
- Sawai, H., Okamoto, Y., Luberto, C., Mao, C., Bielawska, A., Domae, N., Hannun, Y. A. (2000). Identification of ISC1 (YER019w) as Inositol Phosphosphingolipid Phospholipase C in Saccharomyces cerevisiae. *J. Biol. Chem.* 275: 39793-39798 [Abstract] [Full Text]
- Yang, Z., Liu, S., Chen, X., Chen, H., Huang, M., Zheng, J. (2000). Induction of Apoptotic Cell Death and in Vivo Growth Inhibition of Human Cancer Cells by a Saturated Branched-Chain Fatty Acid, 13-Methyltetradecanoic Acid. *Cancer Res* 60: 505-509 [Abstract] [Full Text]
- Erdreich-Epstein, A., Shimada, H., Groshen, S., Liu, M., Metelitsa, L. S., Kim, K. S., Stins, M. F., Seeger, R. C., Durden, D. L. (2000). Integrins {{alpha}}v{beta}3 and {{alpha}}v{beta}5 Are Expressed by Endothelium of High-Risk Neuroblastoma and Their Inhibition Is Associated with Increased Endogenous Ceramide. *Cancer Res* 60: 712-721 [Abstract] [Full Text]
- Holopainen, J. M., Brockman, H. L., Brown, R. E., Kinnunen, P. K. J. (2001). Interfacial Interactions of Ceramide with Dimyristoylphosphatidylcholine: Impact of the N-Acyl Chain. *Biophys J* 80: 765-775 [Abstract] [Full Text]
- Juo, P., Sue-Ann Woo, M., Kuo, C. J., Signorelli, P., Biemann, H. P., Hannun, Y. A., Blenis, J.

(1999). FADD Is Required for Multiple Signaling Events Downstream of the Receptor Fas. *Cell Growth Differ* 10: 797-804 [Abstract] [Full Text]

- Sée, V., Koch, B., Loeffler, J. P. (2001). C2-ceramide and reactive oxygen species inhibit pituitary adenylate cyclase activating polypeptide (PACAP)-induced cyclic-AMP-dependent signalling pathway. *J Neurochem* 76: 778-788 [Abstract] [Full Text]
- Kajimoto, T., Ohmori, S., Shirai, Y., Sakai, N., Saito, N. (2001). Subtype-Specific Translocation of the {delta} Subtype of Protein Kinase C and Its Activation by Tyrosine Phosphorylation Induced by Ceramide in HeLa Cells. *Mol. Cell. Biol.* 21: 1769-1783 [Abstract] [Full Text]
- Hsu, Y.-W., Chi, K.-H., Huang, W.-C., Lin, W.-W. (2001). Ceramide Inhibits Lipopolysaccharide-Mediated Nitric Oxide Synthase and Cyclooxygenase-2 Induction in Macrophages: Effects on Protein Kinases and Transcription Factors. *The JI* 166: 5388-5397 [Abstract] [Full Text]
- Gudz, T. I., Tserng, K.-Y., Hoppel, C. L. (1997). Direct Inhibition of Mitochondrial Respiratory Chain Complex III by Cell-permeable Ceramide. *J. Biol. Chem.* 272: 24154-24158 [Abstract] [Full Text]
- Nikolova-Karakashian, M., Morgan, E. T., Alexander, C., Liotta, D. C., Merrill Jr., A. H. (1997). Bimodal Regulation of Ceramidase by Interleukin-1beta . IMPLICATIONS FOR THE REGULATION OF CYTOCHROME P450 2C11 (CYP2C11). *J. Biol. Chem.* 272: 18718-18724 [Abstract] [Full Text]
- Carter, A. B., Monick, M. M., Hunninghake, G. W. (1998). Lipopolysaccharide-induced NF-kappa B Activation and Cytokine Release in Human Alveolar Macrophages Is PKC-independent and TK- and PC-PLC-dependent. *Am J Respir Cell Mol Biol* 18: 384-391 [Abstract] [Full Text]
- De Maria, R., Rippo, M. R., Schuchman, E. H., Testi, R. (1998). Acidic Sphingomyelinase (ASM) Is Necessary for Fas-induced GD3 Ganglioside Accumulation and Efficient Apoptosis of Lymphoid Cells. *J. Exp. Med.* 187: 897-902 [Abstract] [Full Text]
- Zhou, H., Summers, S. A., Birnbaum, M. J., Pittman, R. N. (1998). Inhibition of Akt Kinase by Cell-permeable Ceramide and Its Implications for Ceramide-induced Apoptosis. *J. Biol. Chem.* 273: 16568-16575 [Abstract] [Full Text]
- Kaneshiro, E. S. (1998). The Lipids of Pneumocystis carinii. *Clin. Microbiol. Rev.* 11: 27-41 [Abstract] [Full Text]
- Singh, I., Pahan, K., Khan, M., Singh, A. K. (1998). Cytokine-mediated Induction of Ceramide Production Is Redox-sensitive. IMPLICATIONS TO PROINFLAMMATORY CYTOKINE-MEDIATED APOPTOSIS IN DEMYELINATING DISEASES. *J. Biol. Chem.* 273: 20354-20362 [Abstract] [Full Text]
- Bourteele, S., Doppler, H., Horn-Muller, J., Ropke, C., Schwarzmann, G., Pfizenmaier, K., Muller, G. (1998). Tumor Necrosis Factor Induces Ceramide Oscillations and Negatively Controls Sphingolipid Synthases by Caspases in Apoptotic Kym-1 Cells. *J. Biol. Chem.* 273: 31245-31251 [Abstract] [Full Text]
- Xia, P., Gamble, J. R., Rye, K.-A., Wang, L., Hii, C. S. T., Cockerill, P., Khew-Goodall, Y., Bert, A. G., Barter, P. J., Vadas, M. A. (1998). Tumor necrosis factor-alpha induces adhesion molecule expression through the sphingosine kinase pathway. *Proc. Natl. Acad. Sci. U. S. A.* 95: 14196-14201 [Abstract] [Full Text]
- Koga, J., Yamauchi, T., Shimura, M., Ogawa, N., Oshima, K., Umemura, K., Kikuchi, M., Ogasawara, N. (1998). Cerebrosides A and C, Sphingolipid Elicitors of Hypersensitive Cell Death and Phytoalexin Accumulation in Rice Plants. *J. Biol. Chem.* 273: 31985-31991 [Abstract] [Full Text]
- SÉGUI, B., BEZOMBES, C., URO-COSTE, E., MEDIN, J. A., ANDRIEU-ABADIE, N., AUGÉ, N., BROUCHET, A., LAURENT, G., SALVAYRE, R., JAFFRÉZOU, J.-P., LEVADE, T. (2000). Stress-induced apoptosis is not mediated by endolysosomal ceramide. *FASEB J.* 14: 36-47 [Abstract] [Full Text]

- Pallis, M., Russell, N. (2000). P-glycoprotein plays a drug-efflux-independent role in augmenting cell survival in acute myeloblastic leukemia and is associated with modulation of a sphingomyelin-ceramide apoptotic pathway. *Blood* 95: 2897-2904 [Abstract] [Full Text]
- Tvrdik, P., Westerberg, R., Silve, S., Asadi, A., Jakobsson, A., Cannon, B., Loison, G., Jacobsson, A. (2000). Role of a New Mammalian Gene Family in the Biosynthesis of Very Long Chain Fatty Acids and Sphingolipids. *J. Cell Biol.* 149: 707-718 [Abstract] [Full Text]
- Di Bartolomeo, S., Di Sano, F., Piacentini, M., Spinedi, A. (2000). Apoptosis Induced by Doxorubicin in Neurotumor Cells Is Divorced from Drug Effects on Ceramide Accumulation and May Involve Cell Cycle-Dependent Caspase Activation. *J Neurochem* 75: 532-539 [Abstract] [Full Text]
- Pahan, K., Khan, M., Singh, I. (2000). Interleukin-10 and Interleukin-13 Inhibit Proinflammatory Cytokine-Induced Ceramide Production Through the Activation of Phosphatidylinositol 3-Kinase. *J Neurochem* 75: 576-582 [Abstract] [Full Text]
- Mao, C., Xu, R., Bielawska, A., Szulc, Z. M., Obeid, L. M. (2000). Cloning and Characterization of a Saccharomyces cerevisiae Alkaline Ceramidase with Specificity for Dihydroceramide. *J. Biol. Chem.* 275: 31369-31378 [Abstract] [Full Text]
- Beauchamp, M. H., Martinez-Bermudez, A. K., Gobeil, F. Jr., Marrache, A. M., Hou, X., Speranza, G., Abran, D., Quiniou, C., Lachapelle, P., Roberts, J. II, Almazan, G., Varma, D. R., Chemtob, S. (2001). Role of thromboxane in retinal microvascular degeneration in oxygen-induced retinopathy. *J. Appl. Physiol.* 90: 2279-2288 [Abstract] [Full Text]
- Beauchamp, M. H., Martinez-Bermudez, A. K., Gobeil, F. Jr., Marrache, A. M., Hou, X., Speranza, G., Abran, D., Quiniou, C., Lachapelle, P., Roberts, J. II, Almazan, G., Varma, D. R., Chemtob, S. (2001). Role of thromboxane in retinal microvascular degeneration in oxygen-induced retinopathy. *J. Appl. Physiol.* 90: 2279-2288 [Abstract] [Full Text]
- Cairns, C. B., Panacek, E. A., Harken, A. H., Banerjee, A. (2000). Bench to Bedside: Tumor Necrosis Factor-alpha: From Inflammation to Resuscitation. *Acad Emerg Med* 7: 930-941 [Abstract] [Full Text]
- Lian, J. P., Huang, R., Robinson, D., Badwey, J. A. (1998). Products of Sphingolipid Catabolism Block Activation of the p21-Activated Protein Kinases in Neutrophils. *The JI* 161: 4375-4381 [Abstract] [Full Text]
- Ko, Y.-G., Lee, J.-S., Kang, Y.-S., Ahn, J.-H., Seo, J.-S. (1999). TNF-{alpha}-Mediated Apoptosis Is Initiated in Caveolae-Like Domains. *The JI* 162: 7217-7223 [Abstract] [Full Text]
- Yeh, M. W., Kaul, M., Zheng, J., Nottet, H. S. L. M., Thylin, M., Gendelman, H. E., Lipton, S. A. (2000). Cytokine-Stimulated, But Not HIV-Infected, Human Monocyte-Derived Macrophages Produce Neurotoxic Levels of L-Cysteine. *The JI* 164: 4265-4270 [Abstract] [Full Text]
- Mandala, S. M., Thornton, R., Tu, Z., Kurtz, M. B., Nickels, J., Broach, J., Menzeleev, R., Spiegel, S. (1998). Sphingoid base 1-phosphate phosphatase: A key regulator of sphingolipid metabolism and stress response. *Proc. Natl. Acad. Sci. U. S. A.* 95: 150-155 [Abstract] [Full Text]
- Chan, T. A., Morin, P. J., Vogelstein, B., Kinzler, K. W. (1998). Mechanisms underlying nonsteroidal antiinflammatory drug-mediated apoptosis. *Proc. Natl. Acad. Sci. U. S. A.* 95: 681-686 [Abstract] [Full Text]
- Mandala, S. M., Thornton, R., Galve-Roperh, I., Poulton, S., Peterson, C., Olivera, A., Bergstrom, J., Kurtz, M. B., Spiegel, S. (2000). Molecular cloning and characterization of a lipid phosphohydrolase that degrades sphingosine-1- phosphate and induces cell death. *Proc. Natl. Acad. Sci. U. S. A.* 97: 7859-7864 [Abstract] [Full Text]
- Quillet-Mary, A., Jaffrezou, J.-P., Mansat, V., Bordier, C., Naval, J., Laurent, G. (1997). Implication of Mitochondrial Hydrogen Peroxide Generation in Ceramide-induced Apoptosis. *J. Biol. Chem.* 272: 21388-21395 [Abstract] [Full Text]
- Tepper, A. D., Cock, J. G. R. B.-d., de Vries, E., Borst, J., van Blitterswijk, W. J. (1997). CD95/Fas-induced Ceramide Formation Proceeds with Slow Kinetics and Is Not Blocked by

Caspase-3/CPP32 Inhibition. *J. Biol. Chem.* 272: 24308-24312 [Abstract] [Full Text]

- Yamaji, A., Sekizawa, Y., Emoto, K., Sakuraba, H., Inoue, K., Kobayashi, H., Umeda, M. (1998). Lysenin, a Novel Sphingomyelin-specific Binding Protein. *J. Biol. Chem.* 273: 5300-5306 [Abstract] [Full Text]
- Segui, B., Andrieu-Abadie, N., Adam-Klages, S., Meilhac, O., Kreder, D., Garcia, V., Bruno, A. P., Jaffrezou, J.-P., Salvayre, R., Kronke, M., Levade, T. (1999). CD40 Signals Apoptosis through FAN-regulated Activation of the Sphingomyelin-Ceramide Pathway. *J. Biol. Chem.* 274: 37251-37258 [Abstract] [Full Text]
- Liu, Y.-Y., Han, T.-Y., Giuliano, A. E., Hansen, N., Cabot, M. C. (2000). Uncoupling Ceramide Glycosylation by Transfection of Glucosylceramide Synthase Antisense Reverses Adriamycin Resistance. *J. Biol. Chem.* 275: 7138-7143 [Abstract] [Full Text]
- Tani, M., Okino, N., Mori, K., Tanigawa, T., Izu, H., Ito, M. (2000). Molecular Cloning of the Full-length cDNA Encoding Mouse Neutral Ceramidase. A NOVEL BUT HIGHLY CONSERVED GENE FAMILY OF NEUTRAL/ALKALINE CERAMIDASES. *J. Biol. Chem.* 275: 11229-11234 [Abstract] [Full Text]
- Manna, S. K., Mukhopadhyay, A., Aggarwal, B. B. (2000). Human Chorionic Gonadotropin Suppresses Activation of Nuclear Transcription Factor-kappa B and Activator Protein-1 Induced by Tumor Necrosis Factor. *J. Biol. Chem.* 275: 13307-13314 [Abstract] [Full Text]
- Luberto, C., Yoo, D. S., Suidan, H. S., Bartoli, G. M., Hannun, Y. A. (2000). Differential Effects of Sphingomyelin Hydrolysis and Resynthesis on the Activation of NF-kappa B in Normal and SV40-transformed Human Fibroblasts. *J. Biol. Chem.* 275: 14760-14766 [Abstract] [Full Text]
- Cuvillier, O., Edsall, L., Spiegel, S. (2000). Involvement of Sphingosine in Mitochondria-dependent Fas-induced Apoptosis of Type II Jurkat T Cells. *J. Biol. Chem.* 275: 15691-15700 [Abstract] [Full Text]
- Liu, J., Tian, J., Haas, M., Shapiro, J. I., Askari, A., Xie, Z. (2000). Ouabain Interaction with Cardiac Na+/K+-ATPase Initiates Signal Cascades Independent of Changes in Intracellular Na+ and Ca2+ Concentrations. *J. Biol. Chem.* 275: 27838-27844 [Abstract] [Full Text]
- Li, R., Manela, J., Kong, Y., Ladisch, S. (2000). Cellular Gangliosides Promote Growth Factor-induced Proliferation of Fibroblasts. *J. Biol. Chem.* 275: 34213-34223 [Abstract] [Full Text]
- Paris, F., Grassme, H., Cremesti, A., Zager, J., Fong, Y., Haimovitz-Friedman, A., Fuks, Z., Gulbins, E., Kolesnick, R. (2001). Natural Ceramide Reverses Fas Resistance of Acid Sphingomyelinase-/- Hepatocytes. *J. Biol. Chem.* 276: 8297-8305 [Abstract] [Full Text]
- Bulotta, S., Barsacchi, R., Rotiroti, D., Borgese, N., Clementi, E. (2001). Activation of the Endothelial Nitric-oxide Synthase by Tumor Necrosis Factor-alpha . A NOVEL FEEDBACK MECHANISM REGULATING CELL DEATH. *J. Biol. Chem.* 276: 6529-6536 [Abstract] [Full Text]
- Corda, S., Laplace, C., Vicaut, E., Duranteau, J. (2001). Rapid Reactive Oxygen Species Production by Mitochondria in Endothelial Cells Exposed to Tumor Necrosis Factor-alpha Is Mediated by Ceramide. *Am J Respir Cell Mol Biol* 24: 762-768 [Abstract] [Full Text]
- Ogretmen, B., Schady, D., Usta, J., Wood, R., Kraveka, J. M., Luberto, C., Birbes, H., Hannun, Y. A., Obeid, L. M. (2001). Role of Ceramide in Mediating the Inhibition of Telomerase Activity in A549 Human Lung Adenocarcinoma Cells. *J. Biol. Chem.* 276: 24901-24910 [Abstract] [Full Text]
- Siskind, L. J., Colombini, M. (2000). The Lipids C2- and C16-Ceramide Form Large Stable Channels. IMPLICATIONS FOR APOPTOSIS. *J. Biol. Chem.* 275: 38640-38644 [Abstract] [Full Text]
- Gewies, A., Rokhlin, O. W., Cohen, M. B. (2000). Ceramide Induces Cell Death in the Human Prostatic Carcinoma Cell Lines PC3 and DU145 but Does Not Seem to Be Involved in Fas-Mediated Apoptosis. *Lab Invest* 80: 671-676 [Abstract] [Full Text]

- Miller, C. J., Stein, G. H. (2001). Human Diploid Fibroblasts That Undergo a Senescent-like Differentiation Have Elevated Ceramide and Diacylglycerol. *J Gerontol A Biol Sci Med Sci* 56: 8B-20 [Abstract] [Full Text]
- Zhang, Y., Mattjus, P., Schmid, P. C., Dong, Z., Zhong, S., Ma, W.-Y., Brown, R. E., Bode, A. M., Schmid, H. H. O., Dong, Z. (2001). Involvement of the Acid Sphingomyelinase Pathway in UVA-induced Apoptosis. *J. Biol. Chem.* 276: 11775-11782 [Abstract] [Full Text]
- Lee, A. C., Fenster, B. E., Ito, H., Takeda, K., Bae, N. S., Hirai, T., Yu, Z.-X., Ferrans, V. J., Howard, B. H., Finkel, T. (1999). Ras Proteins Induce Senescence by Altering the Intracellular Levels of Reactive Oxygen Species. *J. Biol. Chem.* 274: 7936-7940 [Abstract] [Full Text]
- Subbaramaiah, K., Altorki, N., Chung, W. J., Mestre, J. R., Sampat, A., Dannenberg, A. J. (1999). Inhibition of Cyclooxygenase-2 Gene Expression by p53. *J. Biol. Chem.* 274: 10911-10915 [Abstract] [Full Text]
- DeFreitas, M. F., McQuillen, P. S., Shatz, C. J. (2001). A Novel p75NTR Signaling Pathway Promotes Survival, Not Death, of Immunopurified Neocortical Subplate Neurons. *J. Neurosci.* 21: 5121-5129 [Abstract] [Full Text]
- Cuvillier, O., Rosenthal, D. S., Smulson, M. E., Spiegel, S. (1998). Sphingosine 1-Phosphate Inhibits Activation of Caspases that Cleave Poly(ADP-ribose) Polymerase and Lamins during Fas- and Ceramide-mediated Apoptosis in Jurkat T Lymphocytes. *J. Biol. Chem.* 273: 2910-2916 [Abstract] [Full Text]
- Yoshimura, S.-i., Banno, Y., Nakashima, S., Takenaka, K., Sakai, H., Nishimura, Y., Sakai, N., Shimizu, S., Eguchi, Y., Tsujimoto, Y., Nozawa, Y. (1998). Ceramide Formation Leads to Caspase-3 Activation during Hypoxic PC12 Cell Death. INHIBITORY EFFECTS OF Bcl-2 ON CERAMIDE FORMATION AND CASPASE-3 ACTIVATION. *J. Biol. Chem.* 273: 6921-6927 [Abstract] [Full Text]
- Müller, G., Storz, P., Bourteele, S., Döppler, H., Pfizenmaier, K., Mischak, H., Philipp, A., Kaiser, C., Kolch, W. (1998). Regulation of Raf-1 kinase by TNF via its second messenger ceramide and cross-talk with mitogenic signalling. *EMBO J.* 17: 732-742 [Abstract] [Full Text]
- Liu, B., Andrieu-Abadie, N., Levade, T., Zhang, P., Obeid, L. M., Hannun, Y. A. (1998). Glutathione Regulation of Neutral Sphingomyelinase in Tumor Necrosis Factor-alpha -induced Cell Death. *J. Biol. Chem.* 273: 11313-11320 [Abstract] [Full Text]
- Li, R., Blanchette-Mackie, E. J., Ladisch, S. (1999). Induction of Endocytic Vesicles by Exogenous C6-ceramide. *J. Biol. Chem.* 274: 21121-21127 [Abstract] [Full Text]
- Auge, N., Nikolova-Karakashian, M., Carpentier, S., Parthasarathy, S., Negre-Salvayre, A., Salvayre, R., Merrill, A. H. Jr., Levade, T. (1999). Role of Sphingosine 1-Phosphate in the Mitogenesis Induced by Oxidized Low Density Lipoprotein in Smooth Muscle Cells via Activation of Sphingomyelinase, Ceramidase, and Sphingosine Kinase. *J. Biol. Chem.* 274: 21533-21538 [Abstract] [Full Text]
- Limatola, C., Mileo, A. M., Giovannelli, A., Vacca, F., Ciotti, M. T., Mercanti, D., Santoni, A., Eusebi, F. (1999). The Growth-related Gene Product beta Induces Sphingomyelin Hydrolysis and Activation of c-Jun N-terminal Kinase in Rat Cerebellar Granule Neurones. *J. Biol. Chem.* 274: 36537-36543 [Abstract] [Full Text]
- Luberto, C., Hannun, Y. A. (1998). Sphingomyelin Synthase, a Potential Regulator of Intracellular Levels of Ceramide and Diacylglycerol during SV40 Transformation. DOES SPHINGOMYELIN SYNTHASE ACCOUNT FOR THE PUTATIVE PHOSPHATIDYLCHOLINE-SPECIFIC PHOSPHOLIPASE C?. *J. Biol. Chem.* 273: 14550-14559 [Abstract] [Full Text]
- Boland, M. P., O'Neill, L. A. J. (1998). Ceramide Activates NFkappa B by Inducing the Processing of p105. *J. Biol. Chem.* 273: 15494-15500 [Abstract] [Full Text]
- Xu, J., Yeh, C.-H., Chen, S., He, L., Sensi, S. L., Canzoniero, L. M. T., Choi, D. W., Hsu, C. Y. (1998). Involvement of de Novo Ceramide Biosynthesis in Tumor Necrosis Factor-alpha /Cycloheximide-induced Cerebral Endothelial Cell Death. *J. Biol. Chem.* 273: 16521-16526

[Abstract] [Full Text]
- Perry, S. W., Hamilton, J. A., Tjoelker, L. W., Dbaibo, G., Dzenko, K. A., Epstein, L. G., Hannun, Y., Whittaker, J. S., Dewhurst, S., Gelbard, H. A. (1998). Platelet-activating Factor Receptor Activation. AN INITIATOR STEP IN HIV-1 NEUROPATHOGENESIS. *J. Biol. Chem.* 273: 17660-17664 [Abstract] [Full Text]
- Bose, R., Chen, P., Loconti, A., Grullich, C., Abrams, J. M., Kolesnick, R. N. (1998). Ceramide Generation by the Reaper Protein Is Not Blocked by the Caspase Inhibitor, p35. *J. Biol. Chem.* 273: 28852-28859 [Abstract] [Full Text]
- Bieberich, E., Kawaguchi, T., Yu, R. K. (2000). N-Acylated Serinol Is a Novel Ceramide Mimic Inducing Apoptosis in Neuroblastoma Cells. *J. Biol. Chem.* 275: 177-181 [Abstract] [Full Text]
- LIU, Y.-Y., HAN, T.-Y., GIULIANO, A. E., CABOT, M. C. (2001). Ceramide glycosylation potentiates cellular multidrug resistance. *FASEB J.* 15: 719-730 [Abstract] [Full Text]
- Hanada, K., Hara, T., Nishijima, M. (2000). Purification of the Serine Palmitoyltransferase Complex Responsible for Sphingoid Base Synthesis by Using Affinity Peptide Chromatography Techniques. *J. Biol. Chem.* 275: 8409-8415 [Abstract] [Full Text]
- Holopainen, J. M., Medina, O. P., Metso, A. J., Kinnunen, P. K. J. (2000). Sphingomyelinase Activity Associated with Human Plasma Low Density Lipoprotein. POSSIBLE FUNCTIONAL IMPLICATIONS. *J. Biol. Chem.* 275: 16484-16489 [Abstract] [Full Text]
- Vielhaber, G., Brade, L., Lindner, B., Pfeiffer, S., Wepf, R., Hintze, U., Wittern, K.-P., Brade, H. (2001). Mouse anti-ceramide antiserum: a specific tool for the detection of endogenous ceramide. *Glycobiology* 11: 451-457 [Abstract] [Full Text]
- Soini, Y., Paakko, P., Lehto, V-P. (1998). Histopathological Evaluation of Apoptosis in Cancer. *Am J Pathol* 153: 1041-1053 [Full Text]
- Davaille, J., Gallois, C., Habib, A., Li, L., Mallat, A., Tao, J., Levade, T., Lotersztajn, S. (2000). Antiproliferative Properties of Sphingosine 1-Phosphate in Human Hepatic Myofibroblasts. A CYCLOOXYGENASE-2 MEDIATED PATHWAY. *J. Biol. Chem.* 275: 34628-34633 [Abstract] [Full Text]
- Ariga, T., Jarvis, W. D., Yu, R. K. (1998). Role of sphingolipid-mediated cell death in neurodegenerative diseases. *J. Lipid Res.* 39: 1-16 [Abstract] [Full Text]
- Bodennec, J., Koul, O., Aguado, I., Brichon, G., Zwingelstein, G., Portoukalian, J. (2000). A procedure for fractionation of sphingolipid classes by solid-phase extraction on aminopropyl cartridges. *J. Lipid Res.* 41: 1524-1531 [Abstract] [Full Text]
- Memon, R. A., Holleran, W. M., Uchida, Y., Moser, A. H., Grunfeld, C., Feingold, K. R. (2001). Regulation of sphingolipid and glycosphingolipid metabolism in extrahepatic tissues by endotoxin. *J. Lipid Res.* 42: 452-459 [Abstract] [Full Text]
- Ruvolo, P. P., Gao, F., Blalock, W. L., Deng, X., May, W. S. (2001). Ceramide Regulates Protein Synthesis by a Novel Mechanism Involving the Cellular PKR Activator RAX. *J. Biol. Chem.* 276: 11754-11758 [Abstract] [Full Text]
- Xia, P., Vadas, M. A., Rye, K.-A., Barter, P. J., Gamble, J. R. (1999). High Density Lipoproteins (HDL) Interrupt the Sphingosine Kinase Signaling Pathway. A POSSIBLE MECHANISM FOR PROTECTION AGAINST ATHEROSCLEROSIS BY HDL. *J. Biol. Chem.* 274: 33143-33147 [Abstract] [Full Text]
- Igarashi, J., Thatte, H. S., Prabhakar, P., Golan, D. E., Michel, T. (1999). Calcium-independent activation of endothelial nitric oxide synthase by ceramide. *Proc. Natl. Acad. Sci. U. S. A.* 96: 12583-12588 [Abstract] [Full Text]
- De Nadai, C., Sestili, P., Cantoni, O., Lievremont, J.-P., Sciorati, C., Barsacchi, R., Moncada, S., Meldolesi, J., Clementi, E. (2000). Nitric oxide inhibits tumor necrosis factor-alpha -induced apoptosis by reducing the generation of ceramide. *Proc. Natl. Acad. Sci. U. S. A.* 97: 5480-5485 [Abstract] [Full Text]
- Szabo, I., Lepple-Wienhues, A., Kaba, K. N., Zoratti, M., Gulbins, E., Lang, F. (1998). Tyrosine

kinase-dependent activation of a chloride channel in CD95-induced apoptosis in T lymphocytes. *Proc. Natl. Acad. Sci. U. S. A.* 95: 6169-6174 [Abstract] [Full Text]

- Holopainen, J. M., Angelova, M. I., Kinnunen, P. K. J. (2000). Vectorial Budding of Vesicles by Asymmetrical Enzymatic Formation of Ceramide in Giant Liposomes. *Biophys J* 78: 830-838 [Abstract] [Full Text]
- Huang, H.-W., Goldberg, E. M., Zidovetzki, R. (1999). Ceramides Modulate Protein Kinase C Activity and Perturb the Structure of Phosphatidylcholine/Phosphatidylserine Bilayers. *Biophys J* 77: 1489-1497 [Abstract] [Full Text]
- Huang, C., Ma, W.-y., Ding, M., Bowden, G. T., Dong, Z. (1997). Direct Evidence for an Important Role of Sphingomyelinase in Ultraviolet-induced Activation of c-Jun N-Terminal Kinase. *J. Biol. Chem.* 272: 27753-27757 [Abstract] [Full Text]
- Mao, C., Wadleigh, M., Jenkins, G. M., Hannun, Y. A., Obeid, L. M. (1997). Identification and Characterization of Saccharomyces cerevisiae Dihydrosphingosine-1-phosphate Phosphatase. *J. Biol. Chem.* 272: 28690-28694 [Abstract] [Full Text]
- Yang, J., Duerksen-Hughes, P. J. (2001). Activation of a p53-independent, Sphingolipid-mediated Cytolytic Pathway in p53-negative Mouse Fibroblast Cells Treated with N-Methyl-N-nitro-N-nitrosoguanidine. *J. Biol. Chem.* 276: 27129-27135 [Abstract] [Full Text]
- Kim, S., Fyrst, H., Saba, J. (2000). Accumulation of Phosphorylated Sphingoid Long Chain Bases Results in Cell Growth Inhibition in Saccharomyces cerevisiae. *Genetics* 156: 1519-1529 [Abstract] [Full Text]
- Gulbins, E., Szabo, I., Baltzer, K., Lang, F. (1997). Ceramide-induced inhibition of T lymphocyte voltage-gated potassium channel is mediated by tyrosine kinases. *Proc. Natl. Acad. Sci. U. S. A.* 94: 7661-7666 [Abstract] [Full Text]
- YEN, C.-L. E., MAR, M.-H., MEEKER, R. B., FERNANDES, A., ZEISEL, S. H. (2001). Choline deficiency induces apoptosis in primary cultures of fetal neurons. *FASEB J.* 15: 1704-1710 [Abstract] [Full Text]
- Hida, H., Takeda, M., Soliven, B. (1998). Ceramide Inhibits Inwardly Rectifying K+ Currents via a Ras- and Raf-1-Dependent Pathway in Cultured Oligodendrocytes. *J. Neurosci.* 18: 8712-8719 [Abstract] [Full Text]
- Cheng, J., Park, T.-S., Fischl, A. S., Ye, X. S. (2001). Cell Cycle Progression and Cell Polarity Require Sphingolipid Biosynthesis in Aspergillus nidulans. *Mol. Cell. Biol.* 21: 6198-6209 [Abstract] [Full Text]
- Meldrum, D. R. (1998). Tumor necrosis factor in the heart. *Am. J. Physiol.* 274: 577R-595 [Abstract] [Full Text]
- Jones, B. E., Czaja, M. J. (1998). III. Intracellular signaling in response to toxic liver injury. *Am. J. Physiol.* 275: G874-878 [Abstract] [Full Text]
- Mallampalli, R. K., Peterson, E. J., Carter, A. B., Salome, R. G., Mathur, S. N., Koretzky, G. A. (1999). TNF-alpha increases ceramide without inducing apoptosis in alveolar type II epithelial cells. *Am. J. Physiol.* 276: 481L-490 [Abstract] [Full Text]
- Kalhorn, T., Zager, R. A. (1999). Renal cortical ceramide patterns during ischemic and toxic injury: assessments by HPLC-mass spectrometry. *Am. J. Physiol.* 277: 723F-733 [Abstract] [Full Text]
- Ogretmen, B., Kraveka, J. M., Schady, D., Usta, J., Hannun, Y. A., Obeid, L. M. (2001). Molecular Mechanisms of Ceramide-mediated Telomerase Inhibition in the A549 Human Lung Adenocarcinoma Cell Line. *J. Biol. Chem.* 276: 32506-32514 [Abstract] [Full Text]
- Xu, X., Bittman, R., Duportail, G., Heissler, D., Vilcheze, C., London, E. (2001). Effect of the Structure of Natural Sterols and Sphingolipids on the Formation of Ordered Sphingolipid/Sterol Domains (Rafts). COMPARISON OF CHOLESTEROL TO PLANT, FUNGAL, AND DISEASE-ASSOCIATED STEROLS AND COMPARISON OF SPHINGOMYELIN, CEREBROSIDES, AND CERAMIDE. *J. Biol. Chem.* 276: 33540-33546 [Abstract] [Full Text]

- Kita, K., Kurita, T., Ito, M. (2001). Characterization of the reversible nature of the reaction catalyzed by sphingolipid ceramide N-deacylase: A novel form of reverse hydrolysis reaction. *Eur J Biochem* 268: 592-602 [Abstract] [Full Text]
- Davis, W. Jr., Ronai, Z.'e., Tew, K. D. (2001). Cellular Thiols and Reactive Oxygen Species in Drug-Induced Apoptosis. *J. Pharmacol. Exp. Ther.* 296: 1-6 [Abstract] [Full Text]
- Friant, S., Zanolari, B., Riezman, H. (2000). Increased protein kinase or decreased PP2A activity bypasses sphingoid base requirement in endocytosis. *EMBO J.* 19: 2834-2844 [Abstract] [Full Text]
- Chung, N., Mao, C., Heitman, J., Hannun, Y. A., Obeid, L. M. (2001). Phytosphingosine as a Specific Inhibitor of Growth and Nutrient Import in Saccharomyces cerevisiae. *J. Biol. Chem.* 276: 35614-35621 [Abstract] [Full Text]
- Ferlinz, K., Kopal, G., Bernardo, K., Linke, T., Bar, J., Breiden, B., Neumann, U., Lang, F., Schuchman, E. H., Sandhoff, K. (2001). Human Acid Ceramidase. PROCESSING, GLYCOSYLATION, AND LYSOSOMAL TARGETING. *J. Biol. Chem.* 276: 35352-35360 [Abstract] [Full Text]
- Holthuis, J. C. M., Pomorski, T., Raggers, R. J., Sprong, H., Van Meer, G. (2001). The Organizing Potential of Sphingolipids in Intracellular Membrane Transport. *Physiol. Rev* 81: 1689-1723 [Abstract] [Full Text]
- Bezombes, C., Maestre, N., Laurent, G., Levade, T., Bettaïeb, A., Jaffrézou, J.-p. (1998). Restoration of TNF-{alpha}-induced ceramide generation and apoptosis in resistant human leukemia KG1a cells by the P-glycoprotein blocker PSC833. *FASEB J.* 12: 101-109 [Abstract] [Full Text]
- Watts, G. S., Futscher, B. W., Isett, R., Gleason-Guzman, M., Kunkel, M. W., Salmon, S. E. (2001). cDNA Microarray Analysis of Multidrug Resistance: Doxorubicin Selection Produces Multiple Defects in Apoptosis Signaling Pathways. *J. Pharmacol. Exp. Ther.* 299: 434-441 [Abstract] [Full Text]
- Davis, M. A., Flaws, J. A., Young, M., Collins, K., Colburn, N. H. (2000). Effect of Ceramide on Intracellular Glutathione Determines Apoptotic or Necrotic Cell Death of JB6 Tumor Cells. *Toxicol. Sci.* 53: 48-55 [Abstract] [Full Text]
- UEDA, N., CAMARGO, S. M. R., HONG, X., BASNAKIAN, A. G., WALKER, P. D., SHAH, S. V. (2001). Role of Ceramide Synthase in Oxidant Injury to Renal Tubular Epithelial Cells. *J Am Soc Nephrol* 12: 2384-2391 [Abstract] [Full Text]
- Castillo, S. S., Teegarden, D. (2001). Ceramide Conversion to Sphingosine-1-Phosphate is Essential for Survival in C3H10T1/2 Cells. *J. Nutr.* 131: 2826-2830 [Abstract] [Full Text]
- Wintergerst, E. S., Jelk, J., Rahner, C., Asmis, R. (2000). Apoptosis induced by oxidized low density lipoprotein in human monocyte-derived macrophages involves CD36 and activation of caspase-3. *Eur J Biochem* 267: 6050-6059 [Abstract] [Full Text]
- Senchenkov, A., Litvak, D. A., Cabot, M. C. (2001). Targeting Ceramide Metabolism--a Strategy for Overcoming Drug Resistance. *J Natl Cancer Inst* 93: 347-357 [Abstract] [Full Text]
- Yasuda, S., Kitagawa, H., Ueno, M., Ishitani, H., Fukasawa, M., Nishijima, M., Kobayashi, S., Hanada, K. (2001). A Novel Inhibitor of Ceramide Trafficking from the Endoplasmic Reticulum to the Site of Sphingomyelin Synthesis. *J. Biol. Chem.* 276: 43994-44002 [Abstract] [Full Text]
- Sánchez, C., Galve-Roperh, I., Rueda, D., Guzmán, M. (1998). Involvement of Sphingomyelin Hydrolysis and the Mitogen-Activated Protein Kinase Cascade in the Delta 9-Tetrahydrocannabinol-Induced Stimulation of Glucose Metabolism in Primary Astrocytes. *Mol Pharmacol* 54: 834-843 [Abstract] [Full Text]
- BIRBES, H., EL BAWAB, S., HANNUN, Y. A., OBEID, L. M. (2001). Selective hydrolysis of a mitochondrial pool of sphingomyelin induces apoptosis. *FASEB J.* 15: 2669-2679 [Abstract] [Full Text]
- Zhou, H., Li, X.-M., Meinkoth, J., Pittman, R. N. (2000). Akt Regulates Cell Survival and

Apoptosis at a Postmitochondrial Level. *J. Cell Biol.* 151: 483-494 [Abstract] [Full Text]
- Tonnetti, L., Verí, M.-C., Bonvini, E., D'Adamio, L. (1999). A Role for Neutral Sphingomyelinase-mediated Ceramide Production in T Cell Receptor-induced Apoptosis and Mitogen-activated Protein Kinase-mediated Signal Transduction. *J. Exp. Med.* 189: 1581-1589 [Abstract] [Full Text]
- Wang, X.-Z., Beebe, J. R., Pwiti, L., Bielawska, A., Smyth, M. J. (1999). Aberrant Sphingolipid Signaling Is Involved in the Resistance of Prostate Cancer Cell Lines to Chemotherapy. *Cancer Res* 59: 5842-5848 [Abstract] [Full Text]
- Kimura, K., Bowen, C., Spiegel, S., Gelmann, E. P. (1999). Tumor Necrosis Factor-{{alpha}} Sensitizes Prostate Cancer Cells to {{gamma}}-Irradiation-induced Apoptosis. *Cancer Res* 59: 1606-1614 [Abstract] [Full Text]
- Nava, V. E., Cuvillier, O., Edsall, L. C., Kimura, K., Milstien, S., Gelmann, E. P., Spiegel, S. (2000). Sphingosine Enhances Apoptosis of Radiation-resistant Prostate Cancer Cells. *Cancer Res* 60: 4468-4474 [Abstract] [Full Text]
- Selzner, M., Bielawska, A., Morse, M. A., Rüdiger, H. A., Sindram, D., Hannun, Y. A., Clavien, P.-A. (2001). Induction of Apoptotic Cell Death and Prevention of Tumor Growth by Ceramide Analogues in Metastatic Human Colon Cancer. *Cancer Res* 61: 1233-1240 [Abstract] [Full Text]
- Demidem, A., Morvan, D., Papon, J., De Latour, M., Madelmont, J. C. (2001). Cystemustine Induces Redifferentiation of Primary Tumors and Confers Protection against Secondary Tumor Growth in a Melanoma Murine Model. *Cancer Res* 61: 2294-2300 [Abstract] [Full Text]
- Manggau, M., Kim, D.-S., Ruwisch, L., Vogler, R., Korting, H. C., Schafer-Korting, M., Kleuser, B. (2001). 1{alpha},25-Dihydroxyvitamin D3 Protects Human Keratinocytes from Apoptosis by the Formation of Sphingosine-1-Phosphate. *J Invest Dermatol* 117: 1241-1249 [Abstract] [Full Text]
- Tamura, K., Mitsuhashi, N., Hara-Nishimura, I., Imai, H. (2001). Characterization of an Arabidopsis cDNA Encoding a Subunit of Serine Palmitoyltransferase, the Initial Enzyme in Sphingolipid Biosynthesis. *Plant Cell Physiol* 42: 1274-1281 [Abstract] [Full Text]
- Guicciardi, M. E., Miyoshi, H., Bronk, S. F., Gores, G. J. (2001). Cathepsin B Knockout Mice Are Resistant to Tumor Necrosis Factor-{alpha}-Mediated Hepatocyte Apoptosis and Liver Injury : Implications for Therapeutic Applications. *Am J Pathol* 159: 2045-2054 [Abstract] [Full Text]
- Nagata, S. (1999). FAS LIGAND-INDUCED APOPTOSIS. *Annu. Rev. Genet.* 33: 29-55 [Abstract] [Full Text]
- Wallach, D., Varfolomeev, E. E., Malinin, N. L., Goltsev, Y. V., Kovalenko, A. V., Boldin, M. P. (1999). TUMOR NECROSIS FACTOR RECEPTOR AND Fas SIGNALING MECHANISMS. *Annu. Rev. Immunol.* 17: 331-367 [Abstract] [Full Text]
- Gilchrist, D. G. (1998). PROGRAMMED CELL DEATH IN PLANT DISEASE: The Purpose and Promise of Cellular Suicide. *Annu. Rev. Phytopathol.* 36: 393-414 [Abstract] [Full Text]
- Adachi-Yamada, T., Gotoh, T., Sugimura, I., Tateno, M., Nishida, Y., Onuki, T., Date, H. (1999). De Novo Synthesis of Sphingolipids Is Required for Cell Survival by Down-Regulating c-Jun N-Terminal Kinase in Drosophila Imaginal Discs. *Mol. Cell. Biol.* 19: 7276-7286 [Abstract] [Full Text]
- Kalanj-Bognar, S., Rundek, T., Furac, I., Demarin, V., Cosovic, C. (2002). Leukocyte Lysosomal Enzymes in Alzheimer's Disease and Down's Syndrome. *J Gerontol A Biol Sci Med Sci* 57: B16-21 [Abstract] [Full Text]
- Barak, A., Morse, L. S., Goldkorn, T. (2001). Ceramide: A Potential Mediator of Apoptosis in Human Retinal Pigment Epithelial Cells. *Invest. Ophthalmol. Vis. Sci.* 42: 247-254 [Abstract] [Full Text]
- Jaffrézou, J.-p., Maestre, N., Mas-mansat, V. D., Bezombes, C., Levade, T., Laurent, G. (1998). Positive feedback control of neutral sphingomyelinase activity by ceramide. *FASEB J.* 12: 999-1006 [Abstract] [Full Text]

- De Nadai, C., Sestili, P., Cantoni, O., Lièvremont, J.-P., Sciorati, C., Barsacchi, R., Moncada, S., Meldolesi, J., Clementi, E. (2000). Nitric oxide inhibits tumor necrosis factor-alpha -induced apoptosis by reducing the generation of ceramide. *Proc. Natl. Acad. Sci. U. S. A.* 10.1073/pnas.070062397 [Abstract] [Full Text]
- Kinscherf, R., Claus, R., Wagner, M., Gehrke, C., Kamencic, H., Hou, D., Nauen, O., Schmiedt, W., Kovacs, G., Pill, J., Metz, J., Deigner, H.-p. (1998). Apoptosis caused by oxidized LDL is manganese superoxide dismutase and p53 dependent. *FASEB J.* 12: 461-467 [Abstract] [Full Text]
- JAFFRÉZOU, J.-P., BRUNO, A. P., MOISAND, A., LEVADE, T., LAURENT, G. (2001). Activation of a nuclear sphingomyelinase in radiation-induced apoptosis. *FASEB J.* 15: 123-133 [Abstract] [Full Text]
- ZAGER, R. A., BURKHART, K. M., JOHNSON, A. (2000). Sphingomyelinase and Membrane Sphingomyelin Content: Determinants ofProximal Tubule Cell Susceptibility to Injury. *J Am Soc Nephrol* 11: 894-902 [Abstract] [Full Text]
- Van Brocklyn, J. R., Lee, M.-J., Menzeleev, R., Olivera, A., Edsall, L., Cuvillier, O., Thomas, D. M., Coopman, P. J.P., Thangada, S., Liu, C. H., Hla, T., Spiegel, S. (1998). Dual Actions of Sphingosine-1-Phosphate: Extracellular through the Gi-coupled Receptor Edg-1 and Intracellular to Regulate Proliferation and Survival. *J. Cell Biol.* 142: 229-240 [Abstract] [Full Text]
- Olivera, A., Kohama, T., Edsall, L., Nava, V., Cuvillier, O., Poulton, S., Spiegel, S. (1999). Sphingosine Kinase Expression Increases Intracellular Sphingosine-1-phosphate and Promotes Cell Growth and Survival. *J. Cell Biol.* 147: 545-558 [Abstract] [Full Text]
- Shabbits, J. A., Mayer, L. D. (2002). P-Glycoprotein Modulates Ceramide-mediated Sensitivity of Human Breast Cancer Cells to Tubulin-binding Anticancer Drugs. *Mol Cancer Ther* 1: 205-213 [Abstract] [Full Text]
- Czyborra, P., Saxe, M., Fetscher, C., Meyer zu Heringdorf, D., Herzig, S., Jakobs, K. H., Michel, M. C., Bischoff, A. (2002). Transient relaxation of rat mesenteric microvessels by ceramides. *Br. J. Pharmacol.* 135: 417-426 [Abstract] [Full Text]
- Feldhaus, M. J., Weyrich, A. S., Zimmerman, G. A., McIntyre, T. M. (2002). Ceramide Generation in Situ Alters Leukocyte Cytoskeletal Organization and beta 2-Integrin Function and Causes Complete Degranulation. *J. Biol. Chem.* 277: 4285-4293 [Abstract] [Full Text]
- Cardenas, M. E., Cruz, M. C., Del Poeta, M., Chung, N., Perfect, J. R., Heitman, J. (1999). Antifungal Activities of Antineoplastic Agents: Saccharomyces cerevisiae as a Model System To Study Drug Action. *Clin. Microbiol. Rev.* 12: 583-611 [Abstract] [Full Text]
- Kondo, T., Suzuki, Y., Kitano, T., Iwai, K., Watanabe, M., Umehara, H., Daido, N., Domae, N., Tashima, M., Uchiyama, T., Okazaki, T. (2002). Vesnarinone Causes Oxidative Damage by Inhibiting Catalase Function through Ceramide Action in Myeloid Cell Apoptosis. *Mol Pharmacol* 61: 620-627 [Abstract] [Full Text]
- Tepper, A. D., de Vries, E., van Blitterswijk, W. J., Borst, J. (1999). Ordering of ceramide formation, caspase activation, and mitochondrial changes during CD95- and DNA damage–induced apoptosis. *J. Clin. Invest.* 103: 971-978 [Abstract] [Full Text]
- Jensen, J.-M., Schütze, S., Förl, M., Krönke, M., Proksch, E. (1999). Roles for tumor necrosis factor receptor p55 and sphingomyelinase in repairing the cutaneous permeability barrier. *J. Clin. Invest.* 104: 1761-1770 [Abstract] [Full Text]
- Guicciardi, M. E., Deussing, J., Miyoshi, H., Bronk, S. F., Svingen, P. A., Peters, C., Kaufmann, S. H., Gores, G. J. (2000). Cathepsin B contributes to TNF-{alpha}-mediated hepatocyte apoptosis by promoting mitochondrial release of cytochrome c. *J. Clin. Invest.* 106: 1127-1137 [Abstract] [Full Text]
- Dbaibo, G. S., Pushkareva, M. Y., Rachid, R. A., Alter, N., Smyth, M. J., Obeid, L. M., Hannun, Y. A. (1998). p53-dependent Ceramide Response to Genotoxic Stress. *J. Clin. Invest.* 102: 329-339 [Abstract] [Full Text]

Volume 274, Number 5294, Issue of 13 Dec 1996, pp. 1855-1859.

▲ PAGE TOP

```
Connecting via Winsock to STN

Trying 3106016892...Open

Welcome to STN International!  Enter x:x
Welcome to STN International!  Enter x:
LOGINID:SSSPTA1644PNH
LOGINID:
PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Sep 17   IMSworld Pharmaceutical Company Directory name change
                   to PHARMASEARCH
 NEWS  3  Oct 09   Korean abstracts now included in Derwent World Patents
                   Index
 NEWS  4  Oct 09   Number of Derwent World Patents Index updates increased
 NEWS  5  Oct 15   Calculated properties now in the REGISTRY/ZREGISTRY File
 NEWS  6  Oct 22   Over 1 million reactions added to CASREACT
 NEWS  7  Oct 22   DGENE GETSIM has been improved
 NEWS  8  Oct 29   AAASD no longer available
 NEWS  9  Nov 19   New Search Capabilities  USPATFULL and USPAT2
 NEWS 10  Nov 19   TOXCENTER(SM) - new toxicology file now available on STN
 NEWS 11  Nov 29   COPPERLIT now available on STN
 NEWS 12  Nov 29   DWPI revisions to NTIS and US Provisional Numbers
 NEWS 13  Nov 30   Files VETU and VETB to have open access
 NEWS 14  Dec 10   WPINDEX/WPIDS/WPIX New and Revised Manual Codes for 2002
 NEWS 15  Dec 10   DGENE BLAST Homology Search
 NEWS 16  Dec 17   WELDASEARCH now available on STN
 NEWS 17  Dec 17   STANDARDS now available on STN
 NEWS 18  Dec 17   New fields for DPCI
 NEWS 19  Dec 19   CAS Roles modified
 NEWS 20  Dec 19   1907-1946 data and page images added to CA and CAplus
 NEWS 21  Jan 25   BLAST(R) searching in REGISTRY available in STN on the Web
 NEWS 22  Jan 25   Searching with the P indicator for Preparations
 NEWS 23  Jan 29   FSTA has been reloaded and moves to weekly updates
 NEWS 24  Feb 01   DKILIT now produced by FIZ Karlsruhe and has a new update
                   frequency
 NEWS 25  Feb 19   Access via Tymnet and SprintNet Eliminated Effective 3/31/02

 NEWS EXPRESS  February 1 CURRENT WINDOWS VERSION IS V6.0d,
               CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *
```

FILE 'HOME' ENTERED AT 10:29:11 ON 27 FEB 2002

=> file medline embase biosis scisearch caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.45	0.45

FILE 'MEDLINE' ENTERED AT 10:30:53 ON 27 FEB 2002

FILE 'EMBASE' ENTERED AT 10:30:53 ON 27 FEB 2002

FILE 'BIOSIS' ENTERED AT 10:30:53 ON 27 FEB 2002

FILE 'SCISEARCH' ENTERED AT 10:30:53 ON 27 FEB 2002

FILE 'CAPLUS' ENTERED AT 10:30:53 ON 27 FEB 2002

=> s screening method
L1 32998 SCREENING METHOD

=> s l1 and ehemotherapeutic agent
L2 0 L1 AND EHEMOTHERAPEUTIC AGENT

=> s l1 and chemotherapeutic agent
L3 52 L1 AND CHEMOTHERAPEUTIC AGENT

=> s l3 and sphingomyelinase
L4 1 L3 AND SPHINGOMYELINASE

=> d l4 cbib abs

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2001:593239 Document No. 135:134282 Method and identification of agents for the modulation of acid-**sphingomyelinase**-related apoptosis.
Kolesnick, Richard; Schuchman, Edward H. (USA). U.S. US 6274309 B1 20010814, 21 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-687707 19960726.

AB The present invention relates, first, to methods and compns. for the modulation of acid **sphingomyelinase** (ASM)-related processes, including apoptosis. Such apoptosis can include, but is not limited to, environmental stress-induced apoptosis such as, for example, ionizing radiation and/or **chemotherapeutic agent**-induced apoptosis. Apoptosis can be characterized by a cellular morphol. comprising cellular condensation, nuclear condensation or zeiosis. The present invention further relates to methods for the identification of compds. which modulate (i.e., either increase or decrease) sensitivity to ASM-related processes, including apoptosis. ASM-deficient cell lines from patients with Niemann-Pick disease and ASM-deficient mice were resistant to radiation-induced apoptosis.

=> s l3 and ceramide
L5 1 L3 AND CERAMIDE

=> d l5 cbib abs

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS

2001:593239 Document No. 135:134282 Method and identification of agents for the modulation of acid-sphingomyelinase-related apoptosis. Kolesnick, Richard; Schuchman, Edward H. (USA). U.S. US 6274309 B1 20010814, 21 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-687707 19960726.

AB The present invention relates, first, to methods and compns. for the modulation of acid sphingomyelinase (ASM)-related processes, including apoptosis. Such apoptosis can include, but is not limited to, environmental stress-induced apoptosis such as, for example, ionizing radiation and/or **chemotherapeutic agent**-induced apoptosis. Apoptosis can be characterized by a cellular morphol. comprising cellular condensation, nuclear condensation or zeiosis. The present invention further relates to methods for the identification of compds. which modulate (i.e., either increase or decrease) sensitivity to ASM-related processes, including apoptosis. ASM-deficient cell lines from patients with Niemann-Pick disease and ASM-deficient mice were resistant to radiation-induced apoptosis.

=> d his

(FILE 'HOME' ENTERED AT 10:29:11 ON 27 FEB 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 10:30:53 ON 27 FEB 2002

L1 32998 S SCREENING METHOD
L2 0 S L1 AND EHEMOTHERAPEUTIC AGENT
L3 52 S L1 AND CHEMOTHERAPEUTIC AGENT
L4 1 S L3 AND SPHINGOMYELINASE
L5 1 S L3 AND CERAMIDE

=> s l1 and sphingomyelinase
L6 6 L1 AND SPHINGOMYELINASE

=> dup remove l6
PROCESSING COMPLETED FOR L6
L7 3 DUP REMOVE L6 (3 DUPLICATES REMOVED)

=> d l7 1-3 cbib abs

L7 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS

2001:593239 Document No. 135:134282 Method and identification of agents for the modulation of acid-**sphingomyelinase**-related apoptosis. Kolesnick, Richard; Schuchman, Edward H. (USA). U.S. US 6274309 B1 20010814, 21 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-687707 19960726.

AB The present invention relates, first, to methods and compns. for the modulation of acid **sphingomyelinase** (ASM)-related processes, including apoptosis. Such apoptosis can include, but is not limited to, environmental stress-induced apoptosis such as, for example, ionizing radiation and/or chemotherapeutic agent-induced apoptosis. Apoptosis can be characterized by a cellular morphol. comprising cellular condensation, nuclear condensation or zeiosis. The present invention further relates to methods for the identification of compds. which modulate (i.e., either increase or decrease) sensitivity to ASM-related processes, including apoptosis. ASM-deficient cell lines from patients with Niemann-Pick disease and ASM-deficient mice were resistant to radiation-induced apoptosis.

L7 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS

1999:184150 Document No. 130:205169 Method for treating a subject suffering from conditions associated with an extracellular zinc **sphingomyelinase**. Tabas, Ira; Schissel, Scott L.; Williams, Kevin Jon (The Trustees of Colombia University in the City of New York, USA). PCT Int. Appl. WO 9911283 A1 19990311, 189 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES,

FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US18362 19980904. PRIORITY: US 1997-937234 19970905.

AB The present invention provides for a method for treating a subject suffering from a condition assocd. with an extracellular zinc **sphingomyelinase** activity which comprises administering to the subject an amt. of a zinc **sphingomyelinase** inhibitor effective to decrease extracellular zinc **sphingomyelinase** activity in the subject and thereby treat the subject. The present invention also provides for a method for detg. whether a compd. inhibits an activity of an extracellular zinc **sphingomyelinase** involving ceramide formation which comprises: (a) contacting a sample contg. the zinc **sphingomyelinase** under acidic pH conditions known to be assocd. with the activity of such zinc **sphingomyelinase**, with: (i) a substrate of the zinc **sphingomyelinase** enzyme, and (ii) the compd. being evaluated; (b) measuring the concn. of ceramide in the sample from (a); (c) detg. the amt. of zinc **sphingomyelinase** activity in the sample based upon the concn. of ceramide measured in step (b); and (d) comparing the amt. of **sphingomyelinase** activity detd. in step (c) with the amt. of **sphingomyelinase** activity detd. in the absence of the compd., to det. whether the compd. inhibits the activity of zinc **sphingomyelinase**.

L7 ANSWER 3 OF 3 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 1

81074020 EMBASE Document No.: 1981074020. A **screening method** for bacterial production of **sphingomyelinase**. Malmqvist T.. Dept. Bacteriol., Karolinska Inst., S-104 01 Stockholm, Sweden. FEMS Microbiology Letters 10/1 (91-94) 1981. CODEN: FMLED7. Pub. Country: Netherlands. Language: English.

AB This report describes a specific method for screening for **sphingomyelinase** production by bacteria. The presumptive positive findings obtained with staphylocci isolated from clinical specimens in this screening test was compared with quantitative determinations of their spingomyelinase production when grown in nutrient broth. Enzyme activity was measured by specific hydrolysis of immobilized spingomyelin and by haemolytic titration on sheep erythrocytes.

```
=> s l1 and ceramide
   3 FILES SEARCHED...
L8            5 L1 AND CERAMIDE

=> dup remove l8
PROCESSING COMPLETED FOR L8
L9            5 DUP REMOVE L8 (0 DUPLICATES REMOVED)

=> d l9 1-5 cbib abs
```

L9 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2002 ACS

2001:798284 Document No. 135:352747 G protein-coupled receptor (GPCR) agonists and antagonists, and methods of activating and inhibiting GPCR using them. Kuliopulos, Athan; Covic, Lidija (New England Medical Center, USA). PCT Int. Appl. WO 2001081408 A2 20011101, 60 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US13063

20010423. PRIORITY: US 2000-PV198993 20000421.
AB The invention relates generally to G protein coupled receptors and in particular to agonists and antagonists of G protein receptors and methods of using them. Methods for identification of potential therapeutic agents and treating GPCR-assocd. pathol. are also disclosed.

L9 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2002 ACS
2001:677067 Document No. 135:251931 Function homology **screening method**, and use in identification of drug candidates. Berg, Ellen L.; Butcher, Eugene C.; Melrose, Jennifer; Plavec, Ivan (Bioseek, Inc., USA). PCT Int. Appl. WO 2001067103 A1 20010913, 128 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US7190 20010306. PRIORITY: US 2000-PV186976 20000306; US 2000-PV195672 20000407.
AB A method is provided for screening biol. active agents based on the anal. of complex biol. responses in culture. Methods for selecting cells and culture conditions for such screens are provided, as well as the identification of an optimized set of discrete parameters to be measured, and the use of biomap anal. for rapid identification and characterization of drug candidates, genetic sequences acting pathways, and the like. A feature of the invention is simultaneous screening of a large no. of cellular pathways, and the rapid identification of compds. that cause cellular responses.

L9 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2002 ACS
2001:208507 Document No. 134:234000 Spatially-addressed lipid bilayer arrays and lipid bilayers with addressable confined aqueous compartments. Cremer, Paul S.; Simanek, Eric E.; Yang, Tinglu (The Texas A & M University System, USA). PCT Int. Appl. WO 2001020330 A1 20010322, 87 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US25627 20000918. PRIORITY: US 1999-PV154576 19990917; US 2000-564708 20000504.
AB Disclosed are spatially-addressed arrays of discreet fluid lipid bilayers prepd. by flexible patterning methods that facilitate the compartmentalization of lipid membranes and aq. solns. disposed thereon into discreet, spatially-addressable, microarray partitions, onto specific and discreet locations of a substantially planar solid support. This process can either be used in parallel or sequentially to pattern thousands of distinct membranes on a single "biochip", and to assay pluralities of selected analyte components contacted with the discreet lipid bilayer compartments for one or more target mols. Also provided are biochip microarray systems and methods for their prodn. that comprise arrays of confined aq. compartments disposed upon such compartmentalized lipid bilayers. The aq. compartments are independently addressable, thereby facilitating reagent delivery, reagent extn., anal. probe and high-throughput analyte **screening methods**.

L9 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2002 ACS
2001:593239 Document No. 135:134282 Method and identification of agents for the modulation of acid-sphingomyelinase-related apoptosis. Kolesnick, Richard; Schuchman, Edward H. (USA). U.S. US 6274309 B1 20010814, 21 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-687707 19960726.
AB The present invention relates, first, to methods and compns. for the

modulation of acid sphingomyelinase (ASM)-related processes, including apoptosis. Such apoptosis can include, but is not limited to, environmental stress-induced apoptosis such as, for example, ionizing radiation and/or chemotherapeutic agent-induced apoptosis. Apoptosis can be characterized by a cellular morphol. comprising cellular condensation, nuclear condensation or zeiosis. The present invention further relates to methods for the identification of compds. which modulate (i.e., either increase or decrease) sensitivity to ASM-related processes, including apoptosis. ASM-deficient cell lines from patients with Niemann-Pick disease and ASM-deficient mice were resistant to radiation-induced apoptosis.

L9 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2002 ACS
1999:184150 Document No. 130:205169 Method for treating a subject suffering from conditions associated with an extracellular zinc sphingomyelinase. Tabas, Ira; Schissel, Scott L.; Williams, Kevin Jon (The Trustees of Colombia University in the City of New York, USA). PCT Int. Appl. WO 9911283 A1 19990311, 189 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US18362 19980904. PRIORITY: US 1997-937234 19970905.

AB The present invention provides for a method for treating a subject suffering from a condition assocd. with an extracellular zinc sphingomyelinase activity which comprises administering to the subject an amt. of a zinc sphingomyelinase inhibitor effective to decrease extracellular zinc sphingomyelinase activity in the subject and thereby treat the subject. The present invention also provides for a method for detg. whether a compd. inhibits an activity of an extracellular zinc sphingomyelinase involving **ceramide** formation which comprises: (a) contacting a sample contg. the zinc sphingomyelinase under acidic pH conditions known to be assocd. with the activity of such zinc sphingomyelinase, with: (i) a substrate of the zinc sphingomyelinase enzyme, and (ii) the compd. being evaluated; (b) measuring the concn. of **ceramide** in the sample from (a); (c) detg. the amt. of zinc sphingomyelinase activity in the sample based upon the concn. of **ceramide** measured in step (b); and (d) comparing the amt. of sphingomyelinase activity detd. in step (c) with the amt. of sphingomyelinase activity detd. in the absence of the compd., to det. whether the compd. inhibits the activity of zinc sphingomyelinase.

=> s kolesnick r?/au or schuchman e?/au
L10 962 KOLESNICK R?/AU OR SCHUCHMAN E?/AU

=> s k10 and sphingomyelinase
L11 5 K10 AND SPHINGOMYELINASE

=> dup remove l11
PROCESSING COMPLETED FOR L11
L12 1 DUP REMOVE L11 (4 DUPLICATES REMOVED)

=> d l12 cbib abs

L12 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
2001017223 Document Number: 20453360. PubMed ID: 10998148. Impaired cutaneous permeability barrier function, skin hydration, and **sphingomyelinase** activity in keratin 10 deficient mice. Jensen J M; Schutze S; Neumann C; Proksch E. (Department of Dermatology and Institute of Immunology, University of Kiel, Germany.) JOURNAL OF INVESTIGATIVE DERMATOLOGY, (2000 Oct) 115 (4) 708-13. Journal code: IHZ.

ISSN: 0022-202X. Pub. country: United States. Language: English.

AB Point mutations in the suprabasal cytokeratins 1 (K1) or 10 (**K10**) in humans have been shown to be the cause of the congenital ichthyosis epidermolytic hyperkeratosis. Recently, a **K10** deficient mouse model was established serving as a model for epidermolytic hyperkeratosis. Homozygotes suffered from severe skin fragility and died shortly after birth. Heterozygotes developed hyperkeratosis with age. To see whether phenotypic abnormalities in the mouse model were associated with changes in skin barrier function and skin water content we studied basal transepidermal water loss and capacity for barrier repair after experimental barrier disruption as well as stratum corneum hydration. Also, we determined the activities of acid and neutral **sphingomyelinase** key enzymes of the tumor necrosis factor and interleukin-1 signal transduction pathways generating the ceramides most important for epidermal permeability barrier homeostasis. Neonatal homozygotes showed an 8-fold increase in basal transepidermal water loss compared with wild type controls. Adult heterozygotes exhibited delayed barrier repair after experimental barrier disruption. Stratum corneum hydration was reduced in homozygous and heterozygous mice. Acid **sphingomyelinase** activity, which is localized in the epidermal lamellar bodies and generates ceramides for extracellular lipid lamellae in the stratum corneum permeability barrier, was reduced in homozygous as well as heterozygous animals. Neutral **sphingomyelinase** activity, which has a different location and generates ceramides involved in cell signaling, was increased. The reduction in acid **sphingomyelinase** activity may explain the recently described decreased ratio of ceramides to total lipids in **K10** deficient mice. In summary, our results demonstrate the crucial role of the keratin filament for permeability barrier function and stratum corneum hydration.

```
=> d his

     (FILE 'HOME' ENTERED AT 10:29:11 ON 27 FEB 2002)

     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 10:30:53 ON
     27 FEB 2002
L1         32998 S SCREENING METHOD
L2             0 S L1 AND EHEMOTHERAPEUTIC AGENT
L3            52 S L1 AND CHEMOTHERAPEUTIC AGENT
L4             1 S L3 AND SPHINGOMYELINASE
L5             1 S L3 AND CERAMIDE
L6             6 S L1 AND SPHINGOMYELINASE
L7             3 DUP REMOVE L6 (3 DUPLICATES REMOVED)
L8             5 S L1 AND CERAMIDE
L9             5 DUP REMOVE L8 (0 DUPLICATES REMOVED)
L10          962 S KOLESNICK R?/AU OR SCHUCHMAN E?/AU
L11            5 S K10 AND SPHINGOMYELINASE
L12            1 DUP REMOVE L11 (4 DUPLICATES REMOVED)

=> s l10 and ceramide
L13          449 L10 AND CERAMIDE

=> s l13 and screening compound
L14            0 L13 AND SCREENING COMPOUND

=> dup remove l13
PROCESSING COMPLETED FOR L13
L15          145 DUP REMOVE L13 (304 DUPLICATES REMOVED)

=> s l15 and chemotherapeutics
L16            0 L15 AND CHEMOTHERAPEUTICS

=> s l15 and apoptosis
   1 FILES SEARCHED...
```

2 FILES SEARCHED...
L17 79 L15 AND APOPTOSIS

=> dup remove l17
PROCESSING COMPLETED FOR L17
L18 79 DUP REMOVE L17 (0 DUPLICATES REMOVED)

=> s l18 and sphingomyelinase
3 FILES SEARCHED...
L19 33 L18 AND SPHINGOMYELINASE

=> s l19 and ceramide
L20 33 L19 AND CERAMIDE

=> d l20 1-22 cbib abs

L20 ANSWER 1 OF 33 MEDLINE
2001434346 Document Number: 21214818. PubMed ID: 11313707. Niemann-Pick Disease versus acid **sphingomyelinase** deficiency. Lozano J; Morales A; Cremesti A; Fuks Z; Tilly J L; **Schuchman E**; Gulbins E; **Kolesnick R**. CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 100-3. Journal code: C7U; 9437445. ISSN: 1350-9047. Pub. country: England: United Kingdom. Language: English.

L20 ANSWER 2 OF 33 MEDLINE
2001376289 Document Number: 21316440. PubMed ID: 11287428. **Ceramide** enables fas to cap and kill. Cremesti A; Paris F; Grassme H; Holler N; Tschopp J; Fuks Z; Gulbins E; **Kolesnick R**. (Laboratory of Signal Transduction and Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jun 29) 276 (26) 23954-61. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB Recent studies suggest that trimerization of Fas is insufficient for **apoptosis** induction and indicate that super-aggregation of trimerized Fas might be prerequisite. For many cell surface receptors, cross-linking by multivalent ligands or antibodies induces their lateral segregation within the plasma membrane and co-localization into "caps" on one pole of the cell. In this study, we show that capping of Fas is essential for optimal function and that capping is **ceramide** -dependent. In Jurkat T lymphocytes and in primary cultures of hepatocytes, **ceramide** elevation was detected as early as 15-30 s and peaked at 1 min after CH-11 and Jo2 anti-Fas antibody treatment, respectively. Capping was detected 30 s after Fas ligation, peaked at 2 min, and was maintained at a lower level for as long as 30 min in both cell types. **Ceramide** generation appeared essential for capping. Acid **sphingomyelinase** -/- hepatocytes were defective in Jo2-induced **ceramide** generation, capping, and **apoptosis** , and nanomolar concentrations of C(16)-**ceramide** restored these events. To further explore the role of **ceramide** in capping of Fas, we employed FLAG-tagged soluble Fas ligand (sFasL), which binds trimerized Fas but is unable to induce capping or **apoptosis** in Jurkat cells. Cross-linking of sFasL with M2 anti-FLAG antibody induced both events. Pretreatment of cells with natural C(16)-**ceramide** bypassed the necessity for forced antibody cross-linking and enabled sFasL to cap and kill. The presence of intact sphingolipid-enriched membrane domains may be essential for Fas capping since their disruption with cholesterol-depleting agents abrogated capping and prevented **apoptosis**. These data suggest that capping is a **ceramide** -dependent event required for optimal Fas signaling in some cells.

L20 ANSWER 3 OF 33 MEDLINE
2001342203 Document Number: 21282993. PubMed ID: 11279185. CD95 signaling via **ceramide**-rich membrane rafts. Grassme H; Jekle A; Riehle A; Schwarz H; Berger J; Sandhoff K; **Kolesnick R**; Gulbins E.

(Department of Immunology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jun 8) 276 (23) 20589-96. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Clustering seems to be employed by many receptors for transmembrane signaling. Here, we show that acid **sphingomyelinase** (ASM)-released **ceramide** is essential for clustering of CD95. In vitro and in vivo, extracellularly orientated **ceramide**, released upon CD95-triggered translocation of ASM to the plasma membrane outer surface, enabled clustering of CD95 in sphingolipid-rich membrane rafts and **apoptosis** induction. Whereas ASM deficiency, destruction of rafts, or neutralization of surface **ceramide** prevented CD95 clustering and **apoptosis**, natural **ceramide** only rescued ASM-deficient cells. The data suggest CD95-mediated clustering by **ceramide** is prerequisite for signaling and death.

L20 ANSWER 4 OF 33 MEDLINE

2001331477 Document Number: 21292405. PubMed ID: 11399033. An enzymatic assay for quantifying sphingomyelin in tissues and plasma from humans and mice with Niemann-Pick disease. He X; Chen F; Gatt S; **Schuchman E H.** (Department of Human Genetics, Mount Sinai School of Medicine, New York, New York 10029, USA.) ANALYTICAL BIOCHEMISTRY, (2001 Jun 15) 293 (2) 204-11. Journal code: 4NK; 0370535. ISSN: 0003-2697. Pub. country: United States. Language: English.

AB Sphingomyelin is an important lipid component of cell membranes and lipoproteins which can be hydrolyzed by **sphingomyelinases** into **ceramide** and phosphorylcholine. The type A and B forms of Niemann-Pick disease (NPD) are lipid storage disorders due to the deficient activity of the enzyme acid **sphingomyelinase**, and the resultant accumulation of sphingomyelin in cells and tissues. In this paper we report a new, enzyme-based method to quantify the levels of sphingomyelin in tissues and plasma of normal individuals and NPD patients. The method utilizes **sphingomyelinase** from Bacillus cereus to completely hydrolyze the sphingomyelin into **ceramide**. Quantification of the sphingomyelin-derived **ceramide** is accomplished using Escherichia coli diacylglycerol (DAG) kinase and [gamma-(32)P]ATP. The resulting [(32)P]**ceramide** is quantified using a phosphor-imager system following TLC separation. This procedure allowed quantification of sphingomyelin over a broad range from 10 pmol to 1 nmol. To validate this assay we quantified sphingomyelin in plasma and tissues obtained from normal and NPD mice and humans. The sphingomyelin content in adult homozygous (-/-) or heterozygous (+/-) NPD mouse plasma was significantly elevated compared to that of normal mice (up to twofold). Moreover, the accumulated sphingomyelin in the tissues of NPD mice was 4 to 40 times higher than that in normal mice depending on the tissue analyzed. The sphingomyelin levels in plasma from several type B NPD patients also were significantly elevated compared to normal individuals of the same age. Based on these results we propose that this new, enzyme-based procedure can provide sensitive and reproducible sphingomyelin quantification in tissues and fluids from normal individuals and NPD patients. It could be a useful tool for the diagnosis of NPD and the evaluation of NPD treatment protocols, as well as for the study of **ceramide**-mediated **apoptosis** since the method provides the simultaneous determination of sphingomyelin and **ceramide** in the same lipid extract. Copyright 2001 Academic Press.

L20 ANSWER 5 OF 33 MEDLINE

2001290716 Document Number: 21269394. PubMed ID: 11096096. Natural **ceramide** reverses Fas resistance of acid **sphingomyelinase** (-/-) hepatocytes. Paris F; Grassme H; Cremesti A; Zager J; Fong Y; Haimovitz-Friedman A; Fuks Z; Gulbins E; **Kolesnick R.** (Laboratory of Signal Transduction, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Mar 16) 276 (11) 8297-305. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The role of the second messenger **ceramide** in Fas-mediated death requires clarification. To address this issue, we generated hepatocytes from paired acid **sphingomyelinase** (ASMase; asmase)(+/+) and asmase(-/-) mice. asmase(-/-) hepatocytes, derived from 8-week-old mice, manifested normal sphingomyelin content and normal morphological, biochemical, and biologic features. Nonetheless, ASMase-deficient hepatocytes did not display rapid **ceramide** elevation or **apoptosis** in response to Jo2 anti-Fas antibody. asmase(-/-) hepatocytes were not inherently resistant to **apoptosis** because staurosporine, which did not induce early **ceramide** elevation, stimulated a normal apoptotic response. The addition of low nanomolar quantities of natural C16-**ceramide**, which by itself did not induce **apoptosis**, completely restored the apoptotic response to anti-Fas in asmase(-/-) hepatocytes. Other sphingolipids did not replace natural **ceramide** and restore Fas sensitivity. Overcoming resistance to Fas in asmase(-/-) hepatocytes by natural **ceramide** is evidence that it is the lack of **ceramide** and not ASMase which determines the apoptotic phenotype. The ability of natural **ceramide** to rescue the phenotype without reversing the genotype provides evidence that **ceramide** is obligate for Fas induction of **apoptosis** in hepatocytes.

L20 ANSWER 6 OF 33 MEDLINE

2001213898 Document Number: 21115301. PubMed ID: 11220788. Pivotal role for acidic **sphingomyelinase** in cerebral ischemia-induced **ceramide** and cytokine production, and neuronal **apoptosis**. Yu Z F; Nikolova-Karakashian M; Zhou D; Cheng G; **Schuchman E H**; Mattson M P. (Sanders-Brown Research Center on Aging, University of Kentucky, Lexington 40536, USA.) JOURNAL OF MOLECULAR NEUROSCIENCE, (2000 Oct) 15 (2) 85-97. Journal code: AVM; 9002991. ISSN: 0895-8696. Pub. country: United States. Language: English.

AB Stroke is a major cause of long-term disability, the severity of which is directly related to the numbers of neurons that succumb to the ischemic insult. The signaling cascades activated by cerebral ischemia that may either promote or protect against neuronal death are not well understood. One injury-responsive signaling pathway that has recently been characterized in studies of non-neural cells involves cleavage of membrane sphingomyelin by acidic and/or neutral **sphingomyelinase** (ASMase) resulting in generation of the second messenger **ceramide**. We now report that transient focal cerebral ischemia induces large increases in ASMase activity, **ceramide** levels, and production of inflammatory cytokines in wild-type mice, but not in mice lacking ASMase. The extent of brain tissue damage is decreased and behavioral outcome improved in mice lacking ASMase. Neurons lacking ASMase exhibit decreased vulnerability to excitotoxicity and hypoxia, which is associated with decreased levels of intracellular calcium and oxyradicals. Treatment of mice with a drug that inhibits ASMase activity and **ceramide** production reduces ischemic neuronal injury and improves behavioral outcome, suggesting that drugs that inhibit this signaling pathway may prove beneficial in stroke patients.

L20 ANSWER 7 OF 33 MEDLINE

2001112676 Document Number: 20576386. PubMed ID: 11031259. Cell autonomous **apoptosis** defects in acid **sphingomyelinase** knockout fibroblasts. Lozano J; Menendez S; Morales A; Ehleiter D; Liao W C; Wagman R; Haimovitz-Friedman A; Fuks Z; **Kolesnick R**. (Laboratory of Signal Transduction and Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jan 5) 276 (1) 442-8. Journal code: HIV. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB A body of evidence suggests that stress-induced sphingomyelin hydrolysis to the second messenger **ceramide** initiates **apoptosis** in some cells. Although studies using lymphoblasts from Niemann-Pick disease patients or acid **sphingomyelinase** (ASMase)-deficient

mice have provided genetic support for this hypothesis, these models have not been universally accepted as definitive. Here, we show that mouse embryonic fibroblasts (MEFs) prepared from asmase mice manifest cell autonomous defects in **apoptosis** in response to several stresses. In particular, asmase(-/-) MEFs failed to generate **ceramide** and were totally resistant to radiation-induced **apoptosis** but remained sensitive to staurosporine, which did not induce **ceramide** . asmase(-/-) MEFs were also partially resistant to tumor necrosis factor alpha/ actinomycin D and serum withdrawal. Thus, resistance to **apoptosis** in asmase(-/-) MEFs was not global but rather stress type specific. Most importantly, the sensitivity to stress could be restored in the asmase(-/-) MEFs by administration of natural **ceramide**. Overcoming **apoptosis** resistance by natural **ceramide** is evidence that it is the lack of **ceramide**, not ASMase, that determines **apoptosis** sensitivity. The ability to rescue the apoptotic phenotype without reversing the genotype by the product of the enzymatic deficiency provides proof that **ceramide** is obligate for **apoptosis** induction in response to some stresses.

L20 ANSWER 8 OF 33 MEDLINE

2000187582 Document Number: 20187582. PubMed ID: 10722706. Role of acidic **sphingomyelinase** in Fas/CD95-mediated cell death. Lin T; Genestier L; Pinkoski M J; Castro A; Nicholas S; Mogil R; Paris F; Fuks Z; **Schuchman E H**; **Kolesnick R N**; Green D R. (Department of Cellular Immunology, La Jolla Institute for Allergy and Immunology, San Diego, California 92121, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Mar 24) 275 (12) 8657-63. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Engagement of the Fas receptor has been reported to induce **ceramide** generation via activation of acidic **sphingomyelinase** (aSMase). However, the role of aSMase in Fas-mediated cell death is controversial. Using genetically engineered mice deficient in the aSMase gene (aSMase(-/-)), we found that thymocytes, concanavalin A-activated T cells, and lipopolysaccharide-activated B cells derived from both aSMase(-/-) and aSMase(+/+) mice were equally sensitive to Fas-mediated cell death, triggered by either anti-Fas antibody or Fas ligand in vitro. Similarly, activation-induced **apoptosis** of T lymphocytes was unaffected by the status of aSMase, and aSMase(-/-) mice failed to show immunological symptoms seen in animals with defects in Fas function. In vivo, intravenous injection of 3 microg/25 g mouse body weight of anti-Fas Jo2 antibody into aSMase(-/-) mice failed to affect hepatocyte **apoptosis** or mortality, whereas massive hepatocyte **apoptosis** and animal death occurred in wild type littermates. Animals heterozygous for aSMase deficiency were also significantly protected. Susceptibility of aSMase(-/-) mice to anti-Fas antibody was demonstrated with higher antibody doses (>/=4 microg/25 g mouse). These data indicate a role for aSMase in Fas-mediated cell death in some but not all tissues.

L20 ANSWER 9 OF 33 MEDLINE

2000129045 Document Number: 20129045. PubMed ID: 10667583. Radiation-induced **apoptosis** of endothelial cells in the murine central nervous system: protection by fibroblast growth factor and **sphingomyelinase** deficiency. Pena L A; Fuks Z; **Kolesnick R N**. (Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.) CANCER RESEARCH, (2000 Jan 15) 60 (2) 321-7. Journal code: CNF; 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB Injury to the central nervous system (CNS) by ionizing radiation may be a consequence of damage to the vascular endothelium. Recent studies showed that radiation-induced **apoptosis** of endothelial cells in vitro and in the lung in vivo is mediated by the lipid second messenger **ceramide** via activation of acid **sphingomyelinase** (ASM). This apoptotic response to radiation can be inhibited by basic fibroblast

growth factor or by genetic mutation of ASM. In the CNS, single-dose radiation has been shown to result in a 15% loss of endothelial cells within 24 h, but whether or not this loss is associated with **apoptosis** remains unknown. In the present studies, dose- and time-dependent induction of **apoptosis** was observed in the C57BL/6 mouse CNS. **Apoptosis** was quantified by terminal deoxynucleotidyl transferase-mediated nick end labeling, and specific endothelial **apoptosis** was determined by histochemical double labeling with terminal deoxynucleotidyl transferase-mediated nick end labeling and Lycopersicon esculentum lectin. Beginning at 4 h after single-dose radiation, **apoptosis** was ongoing for 24 h and peaked at 12 h at an incidence of 0.7-1.4% of the total cells in spinal cord sections. Up to 20% of the apoptotic cells were endothelial. This effect was also seen in multiple regions of the brain (medulla, pons, and hippocampus). A significant reduction of radiation-induced **apoptosis** was observed after i.v. basic fibroblast growth factor treatment (0.45-4.5 microg/mouse). Identical results were noted in C3H/HeJ mice. Furthermore, irradiated ASM knockout mice displayed as much as a 70% reduction in endothelial **apoptosis**. This study demonstrates that ionizing radiation induces early endothelial cell **apoptosis** throughout the CNS. These data are consistent with recent evidence linking radiation-induced stress with **ceramide** and suggest approaches to modify the apoptotic response in control of radiation toxicity in the CNS.

L20 ANSWER 10 OF 33 MEDLINE

1999114028 Document Number: 99114028. PubMed ID: 9916990. Stress signals for **apoptosis**: **ceramide** and c-Jun kinase. Basu S; **Kolesnick R**. (Laboratory of Signal Transduction, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.) ONCOGENE, (1998 Dec 24) 17 (25) 3277-85. Ref: 75. Journal code: ONC; 8711562. ISSN: 0950-9232. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Mammalian systems respond to environmental stress by either adapting or undergoing programmed cell death. While there is general agreement that the caspase family of proteases serve as the effectors of the apoptotic death response, the signaling apparatus involved in the decision to activate the caspase system is less clear. In the past few years, the sphingomyelin and c-Jun Kinase (JNK)/Stress-activated Protein Kinase (SAPK) pathways have been linked to the death response in many cellular systems. These signaling systems are found throughout the animal kingdom, and **ceramide** signaling is conserved through yeast. Since yeast do not undergo **apoptosis**, the sphingomyelin pathway appears evolutionarily older than the caspase-mediated death programs. While recent reviews by several groups have broadly surveyed **ceramide** signaling in **apoptosis**, this paper examines the role of **sphingomyelinases** and the JNK/SAPK pathway in coordinate signaling of **apoptosis**.

L20 ANSWER 11 OF 33 MEDLINE

1998441840 Document Number: 98441840. PubMed ID: 9769704. Signaling in and regulation of ionizing radiation-induced **apoptosis** in endothelial cells. Billis W; Fuks Z; **Kolesnick R**. (Laboratory of Signal Transduction, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.) RECENT PROGRESS IN HORMONE RESEARCH, (1998) 53 85-92; discussion 93. Ref: 29. Journal code: R1D; 0404471. ISSN: 0079-9963. Pub. country: United States. Language: English.

AB Exposure of mammalian cells to ionizing radiation leads primarily to DNA damage-induced cell death. The induction of **apoptosis** by ionizing radiation represents an alternative mode to cell kill. Breakdown of sphingomyelin to produce **ceramide** by activation of **sphingomyelinase** is one of the upstream signalling cascades activated in apoptotic cells in response to stimuli such as TNF. Using genetic models of acid **sphingomyelinase** deficiency, the **ceramide** generated by radiation-induced activation of **sphingomyelinase** has been shown to serve as a second messenger in

initiating an apoptotic response. PKC activation represents an upstream anti-apoptotic checkpoint at the **sphingomyelinase** level as well as a checkpoint downstream of **ceramide** generation. The balance between these pro- and anti-apoptotic systems may determine the magnitude of the observed apoptotic response.

L20 ANSWER 12 OF 33 MEDLINE
1998266812 Document Number: 98266812. PubMed ID: 9605775. 12-O-tetradecanoylphorbol-13-acetate-induced **apoptosis** in LNCaP cells is mediated through **ceramide** synthase. Garzotto M; White-Jones M; Jiang Y; Ehleiter D; Liao W C; Haimovitz-Friedman A; Fuks Z; **Kolesnick R**. (Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.) CANCER RESEARCH, (1998 May 15) 58 (10) 2260-4. Journal code: CNF; 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.
AB Protein kinase C (PKC) activation is often antiapoptotic, although in a few cell types PKC initiates **apoptosis** by an unknown mechanism. Recent investigations showed that activation of PKC alpha by 12-O-tetradecanoylphorbol 13-acetate (TPA) induced **apoptosis** in LNCaP prostate cancer cells. The present studies examine the mechanism of this effect and show that de novo **ceramide** generation through the enzyme **ceramide** synthase is required. TPA induced rapid **ceramide** generation, which was detectable by 1 h and increased linearly for 12 h. TPA-induced **apoptosis** was measurable by 12 h and was progressive for 48 h. Investigations into the mechanism of TPA-induced **ceramide** generation revealed that acid and neutral **sphingomyelinase** activities were not enhanced. However, TPA induced an increase in **ceramide** synthase activity that persisted for at least 16 h. Treatment with fumonisin B1, a specific natural inhibitor of **ceramide** synthase, abrogated both **ceramide** production and TPA-induced **apoptosis**. **Ceramide** analogues bypassed fumonisin B1 inhibition to initiate **apoptosis** directly. Thus, **ceramide** appears to be a necessary signal for TPA-induced **apoptosis** in LNCaP cells. This represents the first description of a pathway by which PKC may signal **apoptosis**.

L20 ANSWER 13 OF 33 MEDLINE
1998167926 Document Number: 98167926. PubMed ID: 9500792. Acidic **sphingomyelinase** (ASM) is necessary for fas-induced GD3 ganglioside accumulation and efficient **apoptosis** of lymphoid cells. De Maria R; Rippo M R; **Schuchman E H**; Testi R. (Department of Experimental Medicine and Biochemical Sciences, University of Rome "Tor Vergata," 00133 Rome, Italy.) JOURNAL OF EXPERIMENTAL MEDICINE, (1998 Mar 16) 187 (6) 897-902. Journal code: I2V; 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.
AB **Ceramides** deriving from sphingomyelin hydrolysis are important mediators of apoptotic signals originating from Fas (APO-1/CD95). However, definitive evidence for the role played by individual **sphingomyelinases** is still lacking. We have analyzed lymphoblastoid cell lines derived from patients affected by Niemann Pick disease (NPD), an autosomal recessive disorder caused by loss-of-function mutations within the acidic **sphingomyelinase** (ASM) gene. NPD lymphoblasts, which display normal neutral **sphingomyelinase** activity, fail to activate ASM in response to Fas cross-linking, unlike normal lymphoblasts. NPD lymphoblasts also fail to accumulate GD3 ganglioside, a downstream mediator of **ceramide**-induced cell death (De Maria, R., L. Lenti, F. Malisan, F. D'Agostino, B. Tomassini, A. Zeuner, M.R. Rippo, R. Testi. 1997. Science. 277:1652-1655), and display a substantially inefficient **apoptosis** after Fas cross-linking. Inefficient **apoptosis** is due to lack of ASM activity, because proximal signaling from Fas in NPD lymphoblasts is not impaired and **apoptosis** can be efficiently triggered by passing the ASM defect with exogenous **ceramides**. Moreover, mannose receptor-mediated transfer of ASM into NPD lymphoblasts rescues their ability to transiently activate ASM, accumulate GD3, and rapidly undergo **apoptosis**

after Fas cross-linking. These results provide definitive genetic evidence for the role of ASM in the progression of apoptotic signals originating from Fas.

L20 ANSWER 14 OF 33 MEDLINE

1998044248 Document Number: 98044248. PubMed ID: 9382882. Lipopolysaccharide induces disseminated endothelial **apoptosis** requiring **ceramide** generation. Haimovitz-Friedman A; Cordon-Cardo C; Bayoumy S; Garzotto M; McLoughlin M; Gallily R; Edwards C K 3rd; **Schuchman E H**; Fuks Z; **Kolesnick R**. (Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York 10021, USA.) JOURNAL OF EXPERIMENTAL MEDICINE, (1997 Dec 1) 186 (11) 1831-41. Journal code: I2V; 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB The endotoxic shock syndrome is characterized by systemic inflammation, multiple organ damage, circulatory collapse and death. Systemic release of tumor necrosis factor (TNF)-alpha and other cytokines purportedly mediates this process. However, the primary tissue target remains unidentified. The present studies provide evidence that endotoxic shock results from disseminated endothelial **apoptosis**. Injection of lipopolysaccharide (LPS), and its putative effector TNF-alpha, into C57BL/6 mice induced **apoptosis** in endothelium of intestine, lung, fat and thymus after 6 h, preceding nonendothelial tissue damage. LPS or TNF-alpha injection was followed within 1 h by tissue generation of the pro-apoptotic lipid **ceramide**. TNF-binding protein, which protects against LPS-induced death, blocked LPS-induced **ceramide** generation and endothelial **apoptosis**, suggesting systemic TNF is required for both responses. Acid **sphingomyelinase** knockout mice displayed a normal increase in serum TNF-alpha in response to LPS, yet were protected against endothelial **apoptosis** and animal death, defining a role for **ceramide** in mediating the endotoxic response. Furthermore, intravenous injection of basic fibroblast growth factor, which acts as an intravascular survival factor for endothelial cells, blocked LPS-induced **ceramide** elevation, endothelial **apoptosis** and animal death, but did not affect LPS-induced elevation of serum TNF-alpha. These investigations demonstrate that LPS induces a disseminated form of endothelial **apoptosis**, mediated sequentially by TNF and **ceramide** generation, and suggest that this cascade is mandatory for evolution of the endotoxic syndrome.

L20 ANSWER 15 OF 33 MEDLINE

97267750 Document Number: 97267750. PubMed ID: 9113079. Stress-induced **apoptosis** and the sphingomyelin pathway. Pena L A; Fuks Z; **Kolesnick R**. (Laboratory of Signal Transduction, Memorial Sioan-Kettering Cancer Center, New York, NY 19921, USA.) BIOCHEMICAL PHARMACOLOGY, (1997 Mar 7) 53 (5) 615-21. Ref: 63. Journal code: 9Z4; 0101032. ISSN: 0006-2952. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The sphingomyelin pathway is a ubiquitous, evolutionarily conserved signaling system initiated by hydrolysis of the plasma membrane phospholipid sphingomyelin to generate the second messenger **ceramide**. Sphingomyelin degradation is catalyzed by acid and neutral **sphingomyelinase** (SMase) isoforms. Most, if not all mammalian cells, appear capable of signaling though the sphingomyelin pathway. Diverse receptor types and environmental stresses utilize the sphingomyelin pathway as a downstream effector system. In some cellular systems, **ceramide** initiates differentiation or cell proliferation, while in other systems, **ceramide** signals **apoptosis**. Recent investigations link the activation of neutral SMase to the extracellular signal regulated kinase (ERK) cascade and pro-inflammatory responses, and acid SMase to the stress-activated protein kinase/c-jun kinase (SAPK/JNK) cascade and apoptotic responses. Environmental stresses act directly on membrane to activate acid pH-dependent **sphingomyelinase** (ASMase), whereas cytokine receptors signal ASMase activation through motifs termed death domains.

The present review focuses on mechanisms of activation of ASMase and on **ceramide** signaling of the apoptotic response.

L20 ANSWER 16 OF 33 MEDLINE
96319722 Document Number: 96319722. PubMed ID: 8706124. Acid **sphingomyelinase**-deficient human lymphoblasts and mice are defective in radiation-induced **apoptosis**. Santana P; Pena L A; Haimovitz-Friedman A; Martin S; Green D; McLoughlin M; Cordon-Cardo C; **Schuchman E H**; Fuks Z; **Kolesnick R**. (Laboratory of Signal Transduction, Memorial Sloan-Kettering Cancer Center New York, New York 10021, USA.) CELL, (1996 Jul 26) 86 (2) 189-99. Journal code: CQ4; 0413066. ISSN: 0092-8674. Pub. country: United States. Language: English.
AB Stress is believed to activate **sphingomyelinase** to generate **ceramide**, which serves as a second messenger in initiating the apoptotic response. Conclusive evidence for this paradigm, however, is lacking. In the present study, we used a genetic approach to address this issue directly. We show that lymphoblasts from Niemann-Pick patients, which have an inherited deficiency of acid **sphingomyelinase** activity, fail to respond to ionizing radiation with **ceramide** generation and **apoptosis**. These abnormalities are reversible up on restoration of acid **sphingomyelinase** activity by retroviral transfer of human acid **sphingomyelinase** cDNA. Acid **sphingomyelinase** knockout mice also expressed defects in radiation-induced **ceramide** generation and **apoptosis** in vivo. Comparison with p53 knockout mice revealed that acid **sphingomyelinase**-mediated **apoptosis** and p53-mediated **apoptosis** are likely distinct and independent. These genetic models provide definitive evidence for the involvement of acid **sphingomyelinase** in one form of stress-induced **apoptosis**
.

L20 ANSWER 17 OF 33 MEDLINE
95400295 Document Number: 95400295. PubMed ID: 7670466. Acid **sphingomyelinase** deficient mice: a model of types A and B Niemann-Pick disease. Horinouchi K; Erlich S; Perl D P; Ferlinz K; Bisgaier C L; Sandhoff K; Desnick R J; Stewart C L; **Schuchman E H**
. (Department of Human Genetics, Mount Sinai School of Medicine, New York, New York 10029, USA.) NATURE GENETICS, (1995 Jul) 10 (3) 288-93. Journal code: BRO; 9216904. ISSN: 1061-4036. Pub. country: United States. Language: English.
AB Types A and B Niemann-Pick disease (NPD) result from the deficient activity of acid **sphingomyelinase** (ASM). An animal model of NPD has been created by gene targeting. In affected animals, the disease followed a severe, neurodegenerative course and death occurred by eight months of age. Analysis of these animals showed their tissues had no detectable ASM activity, the blood cholesterol levels and sphingomyelin in the liver and brain were elevated, and atrophy of the cerebellum and marked deficiency of Purkinje cells was evident. Microscopic analysis revealed 'NPD cells' in reticuloendothelial organs and characteristic NPD lesions in the brain. Thus, the ASM deficient mice should be of great value for studying the pathogenesis and treatment of NPD, and for investigations into the role of ASM in signal transduction and **apoptosis**.

L20 ANSWER 18 OF 33 MEDLINE
95382894 Document Number: 95382894. PubMed ID: 7544586. The sphingomyelin signal transduction pathway mediates **apoptosis** for tumor necrosis factor, Fas, and ionizing radiation. **Kolesnick R N**; Haimovitz-Friedman A; Fuks Z. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.) BIOCHEMISTRY AND CELL BIOLOGY, (1994 Nov-Dec) 72 (11-12) 471-4. Ref: 37. Journal code: ALR; 8606068. ISSN: 0829-8211. Pub. country: Canada. Language: English.
AB Recent evidence suggests that tumor necrosis factor alpha, Fas, and ionizing radiation employ the sphingomyelin pathway to trigger **apoptosis**. The sphingomyelin pathway is initiated by hydrolysis of

plasma membrane sphingomyelin to generate **ceramide** via a **sphingomyelinase**. **Ceramide** serves as a second messenger stimulating a cascade of kinases and transcription factors that activate a final common pathway of programmed cell death. The extent to which this signaling system is used in **apoptosis** induced by other toxic modalities is not known, but accumulating evidence suggests that it is a commonly employed pathway that could be exploited therapeutically.

L20 ANSWER 19 OF 33 MEDLINE

95081117 Document Number: 95081117. PubMed ID: 7989341. Attenuation of **ceramide**-induced **apoptosis** by diglyceride in human myeloid leukemia cells. Jarvis W D; Fornari F A Jr; Browning J L; Gewirtz D A; **Kolesnick R N**; Grant S. (Department of Medicine, Medical College of Virginia, Richmond 23298.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Dec 16) 269 (50) 31685-92. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Prior studies demonstrated that increased intracellular availability of **ceramide** induces apoptotic DNA degradation and cell death in the human leukemia cell lines HL-60 and U937 (Jarvis, W. D., Kolesnick, R. N., Fornari, F. A., Traylor, R. S., Gewirtz, D. A., and Grant, S. (1994) Proc. Natl. Acad. Sci. U. S. A. 91, 73-77). The present findings show that diglyceride opposes **ceramide**-related **apoptosis** in HL-60 and U937 cells. Acute (6-12-h) exposure to **sphingomyelinase** (100 milliunits/ml) or synthetic **ceramide** (10 microM) promoted apoptotic degradation of genomic DNA as indicated by (a) the appearance of both approximately 50-kilobase pair (kbp) DNA fragments and approximately 0.2-1.2-kbp DNA fragment ladders on agarose gels, (b) formation and release of small double-stranded DNA fragments, and (c) loss of integrity of bulk DNA. DNA damage was associated with reduced clonogenicity and expression of apoptotic morphology. In contrast, exposure to phospholipase C (0.001-100 milliunits/ml) or synthetic diglyceride (10 microM) failed to promote **apoptosis** and abolished the lethal actions of **ceramide** as defined by each of the indices outlined above. **Ceramide**-related **apoptosis** was also reduced by acute (6-h) exposure to tumor promoters such as phorbol dibutyrate and mezerein and the non-tumor-promoting agent bryostatin 1; conversely, chronic (24-h) pretreatment with these agents failed to modify **ceramide** -mediated cytotoxicity, but abolished the protective actions of diglyceride. These findings demonstrate that diglyceride and pharmacological protein kinase C activators reduce or abolish **ceramide**-mediated **apoptosis** in human leukemia cells and support the concept of a cytoprotective function for protein kinase C in the regulation of leukemic cell survival. In addition, the capacity of diglyceride to prevent very early genomic lesions (e.g. generation of 50-kbp DNA fragments) suggests that acute activation of protein kinase C arrests **apoptosis** at an initial stage.

L20 ANSWER 20 OF 33 MEDLINE

94321907 Document Number: 94321907. PubMed ID: 8046331. Ionizing radiation acts on cellular membranes to generate **ceramide** and initiate **apoptosis**. Haimovitz-Friedman A; Kan C C; Ehleiter D; Persaud R S; McLoughlin M; Fuks Z; **Kolesnick R N**. (Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York 10021.) JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Aug 1) 180 (2) 525-35. Journal code: I2V; 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Recent investigations provided evidence that the sphingomyelin signal transduction pathway mediates **apoptosis** for tumor necrosis factor alpha (TNF-alpha) in several hematopoietic and nonhematopoietic cells. In this pathway, TNF-receptor interaction initiates sphingomyelin hydrolysis to **ceramide** by a **sphingomyelinase**. **Ceramide** acts as a second messenger stimulating a **ceramide** -activated serine/threonine protein kinase. The present studies show that ionizing radiation, like TNF, induces rapid sphingomyelin hydrolysis to **ceramide** and **apoptosis** in bovine aortic endothelial

cells. Elevation of **ceramide** with exogenous **ceramide** analogues was sufficient for induction of **apoptosis**. Protein kinase C activation blocked both radiation-induced sphingomyelin hydrolysis and **apoptosis**, and **apoptosis** was restored by **ceramide** analogues added exogenously. Ionizing radiation acted directly on membrane preparations devoid of nuclei, stimulating sphingomyelin hydrolysis enzymatically through a neutral **sphingomyelinase**. These studies provide the first conclusive evidence that apoptotic signaling can be generated by interaction of ionizing radiation with cellular membranes and suggest an alternative to the hypothesis that direct DNA damage mediates radiation-induced cell kill.

L20 ANSWER 21 OF 33 MEDLINE

94105189 Document Number: 94105189. PubMed ID: 8278410. Induction of apoptotic DNA damage and cell death by activation of the sphingomyelin pathway. Jarvis W D; **Kolesnick R N**; Fornari F A; Traylor R S; Gewirtz D A; Grant S. (Department of Medicine, Medical College of Virginia, Richmond 23298-0230.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Jan 4) 91 (1) 73-7. Journal code: PV3; 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The potential involvement of **ceramide**-related signaling processes in the induction of **apoptosis** by tumor necrosis factor alpha was assessed by multiple biochemical strategies in the human leukemic cell lines HL-60 and U937 and the murine fibrosarcoma cell lines L929/LM and WEHI 164/13. Exposure of these cells to tumor necrosis factor alpha resulted in internucleosomal cleavage of genomic DNA, yielding laddered patterns of oligonucleosomal fragments characteristic of **apoptosis** when resolved by agarose gel electrophoresis; similar responses were observed after exposure to exogenous **sphingomyelinase** or synthetic **ceramides**. Quantitative spectrofluorophotometry demonstrated that these treatments promoted time- and concentration-dependent degradation of DNA, resulting in the formation of and eventual release of small DNA fragments (< or = 3.0 kb). Corresponding damage to bulk DNA was demonstrated by enhanced-fluorescence alkaline unwinding analysis. DNA fragmentation was not induced by phospholipase C or synthetic diglyceride; in fact, the effects of **sphingomyelinase** and **ceramide** were substantially reduced by coexposure to these agents, suggesting opposing roles for diglyceride- and **ceramide**-mediated signals in the regulation of **apoptosis**. Phospholipase A2 and arachidonic acid failed to promote DNA fragmentation, as did phospholipase D. Characterization of DNA strand breaks by alkaline and neutral elution analyses confirmed that **ceramide** action was restricted to breakage of mature, double-stranded DNA but not of nascent DNA. The induction of DNA damage was associated with appearance of apoptotic morphology and decreased clonogenicity. These results demonstrate that the **ceramide** -dependent signaling system selectively induces **apoptosis** and raise the possibility that **ceramide**-activated enzymes represent important components in a signaling cascade involved in the regulation of programmed cell death.

L20 ANSWER 22 OF 33 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2001071586 EMBASE Niemann-Pick Disease versus acid **sphingomyelinase** deficiency [1]. Lozano J.; Morales A.; Cremesti A.; Fuks Z.; Tilly J.L.; **Schuchman E.**; Gulbins E.; **Kolesnick R.**. R. Kolesnick, Laboratory of Signal Transduction, Mem. Sloan-Kettering Cancer Ctr., 1275 York Avenue, New York, NY 10021, United States. Cell Death and Differentiation 8/1 (100-102) 2001.
Refs: 29.
ISSN: 1350-9047. CODEN: CDDIEK. Pub. Country: United Kingdom. Language: English.

```
=> s stauropine and apoptosis
L21           0 STAUROPINE AND APOPTOSIS

=>

---Logging off of STN---


=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY     SESSION
FULL ESTIMATED COST                                  107.00      107.45

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY     SESSION
CA SUBSCRIBER PRICE                                   -5.58       -5.58

STN INTERNATIONAL LOGOFF AT 11:01:45 ON 27 FEB 2002
```